Impact that Lack of Access to EGFR Inhibitors has on Progression-Free Survival in Non-Small Cell Lung Cancer treated via the Public Health Care System in Brazil

Abstract

Introduction: The advent of targeted anti-epidermal growth factor receptor (anti-EGFR) therapies has improved survival in patients with metastatic non-small cell lung cancer that carry the EGFR mutation, including those treated via the Brazilian Sistema Único de Saúde (SUS, Unified Health Care System). Objective: To estimate the impact that lack of access to anti-EGFR therapies has on progression-free survival (PFS) among such patients. Method: On the basis of epidemiologic data obtained from the José Alencar Gomes da Silva National Cancer Institute and from studies reporting the prevalence of the EGFR mutation in the Brazilian population, we estimated the number of patients with advanced lung adenocarcinoma and the EGFR mutation who were candidates for targeted therapy in 2017. To estimate effectiveness, we evaluated four different treatments: chemotherapy, erlotinib, afatinib, and gefitinib. The number of patients with PFS after 2 years of follow-up was estimated on the basis of the results of randomized clinical trials. Results: We evaluated 1,735 patients with EGFR mutation-positive metastatic lung adenocarcinoma in Brazil in 2017. We estimated that, if treated with chemotherapy, only 71 of those patients would be free of progression after 24 months. In contrast, if all of the patients were treated with anti-EGFR tyrosine kinase inhibitors, the expectation was that PFS would be achieved in 312 patients for erlotinib, 377 for gefitinib, and 388 for afatinib. Conclusion: Although recommended by international guidelines, anti-EGFR therapies are not available via the SUS, which offers only chemotherapy. This complicates the problem of lack of access in the SUS and promotes local discussion in the public sphere about the incorporation of these therapies.

Key words: Lung Neoplasms; Unified Health Care System; Genes, erbB-1.

Impacto na Sobrevivência Livre de Progressão pela Falta de Acesso a Inhibidores de EGFR em Carcinoma de Pulmão de Células não Pequenas no Sistema de Saúde Pública Brasileiro

Impacto en la Sobrevivencia Libre de Progresión por la Falta de Acceso a los Inhibidores de EGFR en el Carcinoma de Pulmón de Células no Pequeñas en el Sistema de Salud Pública Brasileña

Resumo

Introdução: O advento de terapias-alvo antirreceptor do fator de crescimento epidérmico (anti-eGFr) impactou na sobrevida dos pacientes com câncer de pulmão de células pequenas avançado e portadores de mutação no eGFr, que são tratados no Sistema Único de Saúde Brasileiro (SUS). Objetivo: Estimar o impacto da falta de acesso a terapias anti-eGFr na sobrevida livre de progressão (SLP) desses pacientes. Método: Por meio da base de dados do Instituto Nacional de Câncer José Alencar Gomes da Silva e de estudos que descrevem a prevalência de mutação em eGFr na população brasileira, foi estimado o número de pacientes com adenocarcinoma de pulmão avançado, portadores de mutação eGFr, candidatos à terapia-alvo no ano de 2017. Para a estimativa de efetividade, quatro diferentes esquemas de tratamentos foram considerados: quimioterapia, erlotinib, afatinib e gefitinib. O número de pacientes livres de progressão de doença, após dois anos, foi estimado com base nos resultados para SLP em ensaios clínicos randomizados. Resultados: Foram estimados 1,735 pacientes com adenocarcinoma de pulmão metastático portadores de mutações ativadoras de eGFr no Brasil para o ano de 2017. Projetou-se que, caso fossem tratados com quimioterapia, apenas 71 estariam livres de progressão após 24 meses do início do tratamento. Em contrapartida, com o uso de inibidores de tirosina-quinase anti-eGFr, a expectativa seria de 312 pacientes livres de doença para erlotinib, 377 para gefitinib e 388 para afatinib. Conclusão: Apesar de recomendadas internacionalmente, as terapias anti-eGFr não são disponibilizadas no SUS, sendo oferecidas aos pacientes apenas a quimioterapia. Isso problematiza a situação de falta de acesso no âmbito do SUS e embasa, localmente, a discussão acerca da incorporação dessas terapias no âmbito público.

Palavras-chave: Neoplasias Pulmonares; Sistema Único de Saúde; Genes erbB-1.

Resumen

Introducción: El advenimiento de terapias objetivo anti receptor del factor de crecimiento epidérmico (EGFR) impactó en la supervivencia de los pacientes con cáncer de pulmón de células pequeñas avanzado y portadores de mutación en el EGFR, que son tratados en el sistema único de salud brasileño (SUS). Objetivo: Estimar el impacto de la falta de acceso a terapias anti-EGFR en la sobrevida libre de progresión (SLP) de esos pacientes. Método: A través de la base de datos del Instituto Nacional de Cáncer José Alencar Gomes da Silva y de estudios que describen la prevalencia de mutación de EGFR en la población brasileña, se estima el número de pacientes con adenocarcinoma de pulmón avanzado portadores de mutación EGFR candidatos a la terapia objetivo en el año de Para la estimación de efectividad, cuatro diferentes esquemas de tratamientos fueron considerados: quimioterapia, erlotinib, afatinib y gefitinib. El número de pacientes libres de progresión de la enfermedad después de dos años se calculó sobre la base de los resultados para SLP en los ensayos clínicos aleatorizados. Resultados: Se estimó 1.735 pacientes con adenocarcinoma de pulmón metastático, portadores de mutaciones activadoras de EGFR en Brasil para el año 2017. Se proyectó que si se trataran con quimioterapia sólo 81 estarían libres de progresión después de 24 meses. En contrapartida, con el uso de inhibidores de tirosina quinasa anti-EGFR, la expectativa sería de 312 pacientes libres de enfermedad para erlotinib, 377 para gefitinib y 388 para afatinib. Conclusión: A pesar de ser recomendadas internacionalmente, las terapias anti-EGFR no están disponibles en el SUS, siendo ofrecido a los pacientes sólo quimioterapia. Esto problematiza claramente la situación de falta de acceso en el ámbito del SUS y basan, localmente, la discusión sobre la incorporación de estas terapias en el ámbito público.

Palabras clave: Neoplasias Pulmonares; Sistema Único de Salud; Genes erbB-1.

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INTRODUCTION

Lung cancer is the leading malignant neoplasm worldwide\(^1\). In Brazil, it is a major public health problem, with annual estimates of 28,220 new cases and 24,490 deaths\(^2\).

Non-small cell lung cancer (NSCLC) accounts for 85% of primary lung neoplasms, most patients (44%) being diagnosed in advanced stages\(^1,3\). For such patients, palliative systemic treatment is the main therapeutic option. With advances in molecular diagnostic techniques, targeted therapies that are more effective and less toxic than chemotherapy are now available for patients with epidermal growth factor receptor (EGFR)-activating mutations and anaplastic lymphoma kinase (ALK) translocation, for example\(^4\). In a study conducted by Midha et al.\(^5\), the estimated prevalence of EGFR-activating mutations among patients with advanced lung adenocarcinoma in the population of Brazil was 28%.

After anti-EGFR tyrosine kinase inhibitors (TKI) had been shown to be more efficacious and less toxic than cytotoxic chemotherapy as a first-line palliative treatment in patients with advanced lung adenocarcinoma, the U.S. Food and Drug Administration (FDA) approved different drugs for that purpose\(^6,7\): erlotinib, in May 2013; afatinib, in July 2013; and gefitinib, in June 2015. However, clinical studies evaluating these drugs have demonstrated significant benefits in progression-free survival (PFS), although without an increase in overall survival (OS) when compared with standard chemotherapy\(^8\).

The Brazilian Sistema Único de Saúde (SUS, Unified Health Care System) limits access to TKI. Although they were approved by the Comissão Nacional de Incorporação de Tecnologias no SUS (Conitec, National Commission for the Incorporation of Health Technologies into the SUS) for patients with EGFR mutation-positive stage IV NSCLC, these drugs are not effectively available to their users in Brazil, because of the lack of a specific budget and transfer of resources that cover their costs, except in the state of São Paulo. Therefore, patients gain access to these medications through petitions filed with the judicial system. The present study aims to estimate the impact that the lack of access to anti-EGFR therapies has on PFS in patients with EGFR mutation-positive metastatic NSCLC treated via the SUS.

METHOD

The number of patients eligible for TKI therapy in 2017 was estimated from the prevalence and incidence of lung cancer data published by the Instituto Nacional de Cáncer José Alencar Gomes da Silva (INCA, José Alencar Gomes da Silva National Cancer Institute), in its cancer incidence estimate report for the 2016–2017 biennium\(^3\). The portion of the population with access to supplementary health plans, either private plans or plans exclusively for public servants, as identified on the basis of data from the Instituto Brasileiro de Geografia e Estatística (IBGE, Brazilian Institute of Geography and Statistics), was excluded from the analysis, because it was not the target audience of this analysis\(^9\). Because the prevalence data for EGFR-activating mutations, required for the use of TKI, refer to the adenocarcinoma histology, only that subtype was considered\(^5\). The estimated number of patients with metastatic disease was determined by adding the estimated number of patients diagnosed in clinical stage IV (CS IV)\(^3\) in 2017 to the estimated number of patients diagnosed in the previous five years and experiencing recurrence in 2017. For that purpose, a five-year recurrence rate was assigned to patients diagnosed in CS I, II, or III, based on their prognosis\(^10\).

The incidence of Brazilian patients with EGFR mutation-positive adenocarcinoma was obtained from the study conducted by Midha et al.\(^5\). Figure 1 summarizes the methodology used in order to estimate the number of patients with advanced lung cancer who were candidates for anti-EGFR therapy.

The estimated number of patients with PFS after two years was obtained by applying the estimates of PFS rates after 24 months of follow-up, based on the results reported in the Eurtac, LUX-Lung 3, and

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**Figure 1.** Patients with advanced EGFR mutation-positive lung adenocarcinoma treated via the SUS in 2017

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LUX-Lung 7 studies\textsuperscript{11-13}, for erlotinib, afatinib, and gefitinib, respectively. The PFS rate for chemotherapy was obtained by taking into consideration the control (platinum-based polychemotherapy) arm of the Eurtac study\textsuperscript{11}.

The design of the present study was that of a mixed original article, based on statistical estimates and calculations, always in view of previously published data. Therefore, on the basis of Brazilian Platform Resolution no. 466, there was no need for approval by the local research ethics committee.

**RESULTS**

According to INCA estimates, there are 28,220 new cases of lung cancer annually in Brazil\textsuperscript{5}. Of those, 76.3\% are treated via the SUS, totaling 21,532 cases\textsuperscript{8}. According to the American Cancer Society\textsuperscript{3,14}, 40\% of lung cancer patients have adenocarcinoma (40\% of 21,532 = 8,613 patients) and 44\% of those patients present in CS IV (44\% of 8,613 = 3,790 patients). Patients who were diagnosed in stages I through III in the previous five years and tended to experience recurrence in 2017 were added to this result. The five-year recurrence rate is 53.79\% for CS III, 46.49\% for CS II, and 26.06\% for CS I\textsuperscript{10}. Based on those rates, an estimated 2,407 patients were diagnosed with recurrence in 2017, which, together with those diagnosed in CS IV, totaled 6,197 cases of advanced lung adenocarcinoma treated via the SUS in that year. Of those, 28\% were assumed to have an EGFR-activating mutation, resulting in 1,735 patients who were candidates for anti-EGFR therapy\textsuperscript{5}. Table 1 summarizes these results.

Assuming that all these patients receive platinum-based chemotherapy (the SUS-approved treatment) and applying a rate of 12.48\% to the monthly number of patients with disease progression (the same as that observed in the Eurtac study), only 71 individuals would be free of progression after two years. For that last estimate, the proportion of patients with disease progression throughout the treatment was considered to be constant. In contrast, we estimated that a greater number of individuals in the present study would have been free of disease progression during the two-year follow-up period, based on the same methodology, if the treatments of choice had been available for this population 377 for gefitinib, 388 for afatinib, and 312 for erlotinib, translating to monthly progression rates of 6.16\%, 6.05\%, and 6.90\%, respectively, as depicted in Figure 2.

**DISCUSSION**

Targeted therapy is a breakthrough in fighting cancer from the last century. The idea of selecting a specific cancer cell molecule as the therapeutic focus dates back to 1997, with the FDA approval of the monoclonal antibody rituximab against non-Hodgkin lymphoma, the main exponent of which is trastuzumab,
another monoclonal antibody, approved in 1999, for the treatment of breast cancer.

The most relevant target molecule in pulmonary neoplasms is EGFR. In the Eurtac study, a TKI was used successfully to treat lung cancer in patients with an EGFR mutation. The FDA recently approved three drugs as first-line treatments in patients with EGFR mutation-positive metastatic non-squamous cell lung cancer: erlotinib, afatinib, and gefitinib. These drugs, in comparison with chemotherapy, have been shown to provide longer PFS and to have lower toxicity.

The advent of targeted therapies has resulted in great progress in the treatment of lung cancer over the last decades, with a significant increase in survival. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the U.S. National Cancer Institute show that, among lung cancer patients, 12-, 24-, and 60-month survival increased from 29.3%, 16.4%, and 9.0%, respectively, in 1973 to 46.5%, 30.0%, and 17.0%, respectively, in 2013. However, lung cancer continues to be the primary neoplasm with the highest mortality worldwide.

Randomized controlled trials (RCT) of TKI have not shown a gain in OS among patients with lung cancer. However, it is worth noting that, although TKI treatment does not increase OS, PFS is now accepted as a parameter for the evaluation and consequent approval of new therapeutic modalities. According to the literature, PFS is used as the primary endpoint in 51% of studies. In addition, there is a statistically significant correlation between OS and PFS, the latter being accepted as a surrogate for the former. It was on the basis of this argument that several studies have used PFS as a primary outcome in their results, such as those related to the use of bevacizumab (against renal cell carcinoma) and crizotinib (against lung cancer).

However, the reality in Brazil is that only a minority of the population has access to more complex treatments, especially in the area of oncology. The public health care system of the country has two forms of funding: public, via the SUS; and private, via the supplementary health care system. Each of those covers approximately 50% of all health care expenditures. However, the portion of the population that depends on public funding is 74.3%. The consequence of this funding model, in which the private health care market effectively has a per capita expenditure three times that of the public health care market, is health care inequality.

For patients covered by the supplementary health care system, the drugs, as soon as they are regularized and approved by the Brazilian Agência Nacional de Vigilância Sanitária (Anvisa, National Health Oversight Agency), are soon granted. For patients who are dependent exclusively on the public system, the reality is different. The Brazilian National Ministry of Health (NMH) finances cancer drugs in two ways: centralized purchasing, and Authorization of Procedimentos Ambulatoriais de Alta Complexidade/Custos (Apac, Authorization of High-Complexity/Cost Outpatient Procedures). In the first case, some medications, such as trastuzumab and rituximab, are provided free of charge by the system itself. In contrast, the Apac covers the vast majority of drugs. In this form of costing, there is a fixed amount, previously established by the NMH, provided to finance the treatment provided by the hospital.

In both forms of NMH funding for cancer drugs, is necessary to obtain the approval of Anvisa, which evaluates the effectiveness and safety of the drugs. It is also essential to obtain permission from the Conitec, which carries out a cost-benefit analysis to decide whether or not the treatment should be provided by the government.

Indeed, just as Anvisa had already done, Conitec approved the incorporation of erlotinib and gefitinib into the SUS, in November 2013. However, those treatments depend on the Apac model of funding. The point of interest of the present study is that, in this form of funding, there are certain cases in which the costs passed on to the hospital to the treatment offered do not necessarily fully cover the expenditures incurred by the health care facility. Thus, there is a clear disincentive to seek treatments that are not adequately funded, and the drugs that form the basis of this study – gefitinib and erlotinib – are examples of such practices. It is practically impossible for public hospitals to offer those drugs to patients who do not have private health insurance.

For the treatment of patients with EGFR mutation-positive metastatic NSCLC, there is a certain divergence between what is called for in international protocols and what is offered to Brazilian citizens who are dependent on the public health care system. From that perspective, treatment with standard chemotherapy has negative consequences that do not occur after treatment with TKI, this being the main factor that our study aimed to elucidate.

The results of the present study indicate that, of the patients diagnosed in 2017, up to 388 patients would be free of disease progression at the end of two years if all of the patients had undergone treatment with the therapies targeting EGFR mutations, compared with only 71 patients if they had all been submitted to the treatment provided by the SUS.

We now know that, in addition to doctors and patients, the pharmaceutical industry and government agencies have considerable influence over whether a
drug is universally incorporated. From that perspective, a study that attempts to show the consequences of depriving a certain population of a given drug can also do much to influence those choices.

This analysis has significant limitations. For example, epidemiological data for Brazil are often scarce. That is why we used the INCA estimates as the basis for our analysis. In addition, it is known that a prevalence of EGFR-activating mutations of 28% represents an overestimation. However, for calculation purposes, that was the value chosen for our estimations. Furthermore, our data were related only to patients diagnosed with advanced disease. The prognosis of recurrence was based on a study conducted in the United States, in which the treatments available for that population were not necessarily the same as those available for our study population. Moreover, we observed differences in PFS greater than those reported directly from RCT, and it is possible that such differences are not as pronounced in clinical practice. That assumption could introduce a bias favoring a difference between treatments in real life.

**CONCLUSION**

Generally speaking, six years after the publication of the Eurtac study, the SUS had not yet definitively included TKI in the table of drugs made available to the population. Their introduction could increase PFS among patients with EGFR mutation-positive metastatic NSCLC in Brazil. The results of the present study indicate that, over a period two years, the use of TKI could halt progression of the disease in at least 317 patients.

**AUTHOR CONTRIBUTIONS**

Gabriel Lenz and Leonardo Stone Lago conceived and designed the study; analyzed and interpreted the data; drafted and revised the manuscript; and approved the final version for submission. Rodrigo Azevedo Pellegrini conceived and designed the study; and analyzed and interpreted the data. Lana Becker Micheletto drafted and revised the manuscript.

**DECLARATION OF CONFLICTS OF INTEREST**

Nothing to declare.

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