ORIGINAL ARTICLE

Distinct models to assess the cost-effectiveness of EGFR-tyrosine kinase inhibitors for the treatment of metastatic non-small cell lung cancer in the context of the Brazilian Unified Health Care System

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ABSTRACT

Objective: Lung cancer is an important health problem due to its high incidence and mortality. The treatment of metastatic disease improved after the molecular pathways of cancer came to be known. However, targeted therapy is unavailable to many patients treated within the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System). Our objective was to assess the cost-effectiveness of erlotinib, gefitinib, and afatinib versus that of chemotherapy for the treatment of non-small cell lung cancer in the context of the SUS. **Methods:** Different analytical models were developed based on data in the literature. The outcomes were presented in quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) per QALY gained. All costs related to treatment and supportive therapies were included in the models. **Results:** In one model, data from retrospective studies showed 2.01 life-years saved and a mean QALY gain of 1.169. The ICER per QALY gained ranged from R$48,451.29 (for gefitinib) to R$85,559.22 (for erlotinib). In another model, data from a meta-analysis showed −0.01 life-years saved and a mean QALY gain of 0.178. The ICER per QALY gained ranged from R$27,028.30 (for gefitinib) to R$75,203.26 (for erlotinib). **Conclusions:** There is no ideal analytical model for the SUS. However, targeted therapy with EGFR-tyrosine kinase inhibitors has been shown to be cost-effective in various scenarios. The adoption of drug price discounts will improve the cost-effectiveness of treatment.

Keywords: Health policy; Molecular targeted therapy; Economics, pharmaceutical; Brazil.

INTRODUCTION

Lung cancer is the most common cancer worldwide, with more than 1.8 million new cases diagnosed in 2012.[1] In Brazil, despite the potential underestimation of data, 28,220 new cases of and more than 22,000 deaths from lung cancer were expected to occur in 2017.[2]

Most cases of lung cancer (70%) are detected at an advanced stage, when prognosis is poor and 5-year survival is approximately 4%.[3] The standard treatment for advanced lung cancer at all facilities within the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System) continues to be platinum-based chemotherapy, after which median overall survival does not exceed 12 months.[4,5]

At the beginning of the 21st century, knowledge of molecular pathways led to the development of specific therapies and an improvement in outcomes. The therapies most widely studied in non-small cell lung cancer (NSCLC) are those based on EGFR, which is a transmembrane receptor involved in signaling to regulate cell proliferation, angiogenesis, and cell survival.[6] Treatment with tyrosine kinase inhibitors (TKIs) targeting the EGFR pathway has led to a tumor response rate greater than 50% and an increase in median progression-free survival of nearly 100%.[7-9]

Despite its significant benefits, targeted therapy (with EGFR-TKIs) is not yet widely available within the SUS because of its high cost compared with that of chemotherapy. The reimbursement from the SUS, in Brazilian reals (R$), is currently R$1,100.00 for each month of treatment for metastatic lung cancer, whereas the mean monthly cost of therapies with first- and second-generation EGFR-TKIs ranges from R$2,700.00 to R$5,600.00. The manager of each facility within the SUS is charged with identifying solutions for incorporating targeted therapy. The main options are to include in the facility budget the difference between the cost of targeted therapy and the amount reimbursed by the SUS or negotiate with manufacturers for a price that is consistent with the amount reimbursed by the SUS.

Given all of the above, our hypothesis was that molecular targeted therapy may be cost-effective for the treatment of NSCLC in Brazil. In addition, strategies that lead to a reduction in the cost of EGFR-TKIs may

further improve the cost-effectiveness of targeted therapy compared with that of chemotherapy and increase the availability of targeted therapy to patients treated within the SUS.

Data from randomized clinical trials differ from those describing the current context of the SUS.[7-9] The first difference relative to the current practice within the SUS is that, in those studies, all patients were tested for *EGFR* mutations and only *EGFR* mutation-positive patients were included.[7,8] In addition, all such trials have shown a high degree of overlap (approximately 70%) between the study arms; that is, most patients received first- or second-line molecular targeted therapy and therefore no gain in overall survival was observed.[7-9] In order to provide a view complementary to that of randomized clinical trials,[7-9] we developed distinct models based on data from the literature that are closest to the current reality in Brazil.

The primary objective of the present study was to calculate the incremental cost-effectiveness ratio (ICER) for targeted therapy (with EGFR-TKIs) versus chemotherapy in distinct models, in order to understand the cost-effectiveness of EGFR-TKIs for the treatment of advanced NSCLC. The secondary objectives were to identify which variables most influence the cost-effectiveness of targeted therapy and to identify which model is closest to the ideal for the current context of the SUS.

METHODS

We developed two analytical decision models. Each model considered a different strategy based on distinct data from the literature. In all models, deterministic sensitivity analyses were performed to confirm the robustness of the findings

The study considered the current reality of the SUS, including the costs of *EGFR* mutation testing (Sanger DNA sequencing), the purchase of drugs for first- and second-line treatments, monitoring, treatment of adverse events, and supportive therapies.

Structure of the models

In all models, patients were classified into three mutually exclusive health status groups: progression-free survival; post-progression survival; and death.

The first model considered two distinct retrospective studies, both of which involved Asian populations.[10,11] In one study,[10] patients with *EGFR* mutations were treated with first-line EGFR-TKIs, whereas in the other study,[11] *EGFR* mutation testing was not performed and all patients were treated with conventional chemotherapy. In this model, two strategies were compared: testing all patients for *EGFR* mutations and treating *EGFR* mutation-positive patients with first-line EGFR-TKIs and second-line chemotherapy; and not performing *EGFR* mutation testing and treating all patients with chemotherapy in all lines of treatment.

The second model considered data from an individual meta-analysis including the major randomized clinical trials comparing chemotherapy versus EGFR-TKIs in first-line treatment.[12] However, most (74%) of the patients who were randomized to chemotherapy received EGFR-TKIs in second-line treatment. Therefore, in this model, two strategies were compared: testing patients for *EGFR* mutations and treating *EGFR* mutation-positive patients with first-line EGFR-TKIs and second-line chemotherapy; and testing patients for *EGFR* mutations and treating *EGFR* mutation-positive patients with first-line chemotherapy and second-line EGFR-TKIs. The two models are summarized in Figure 1.

Clinical effectiveness and quality of life

Effectiveness data were obtained by comparing the areas under the progression-free and overall survival curves reported in each study used in the distinct models.[10-12] The minimum follow-up time was set at 5 years.

Data on afatinib effectiveness were based on the results of a study that compared afatinib with gefitinib and demonstrated that both had similar efficacy, with a small benefit in terms of progression-free survival for afatinib.[13]

Quality-adjusted life-years (QALYs) for each health status group were calculated from the utility values published in the literature, adjusted for the adverse events provoked by each treatment.[14,15]

Costs

The costs of erlotinib, gefitinib, and afatinib were based on the maximum prices set for their sale to the Brazilian government, which are available on the website of the Brazilian Chamber of Drug Market Regulation.[16]

The cost of chemotherapy, regardless of the agent used or the line of treatment considered, was fixed at the amount paid by the SUS for the treatment of advanced NSCLC (R$1,100.00 per month). The duration of treatment for each pharmacological regimen was linked to progression-free survival for first-line treatments and to post-progression survival for second-line treatments.

We considered the costs of *EGFR* mutation testing (Sanger sequencing) for all patients (considering that for each test with a positive result, three tests with a negative result will also be paid for). The costs of treatment of adverse events and supportive therapies were calculated from values available in the Brazilian literature.[17,18]

Deterministic sensitivity analyses

We performed univariate deterministic sensitivity analysis (DSA) in all models. We used 95% CIs or plausible ranges (when the 95% CI was unavailable). Table 1 summarizes the variables considered in the DAS.

RESULTS

Retrospective study model

Compared with the strategy of not testing for EGFR mutations and treating all patients with chemotherapy, that of testing for *EGFR* mutations and administering targeted therapy to *EGFR* mutation-positive patients saved 2.01 life-years.

In the base case, erlotinib lead to a QALY gain of 1.169 at a mean incremental cost per patient of R$100,000.67, which resulted in an ICER per QALY gained of R$85,559.22 and an incremental cost per life-year saved of R$49,730.96. Gefitinib led to a QALY gain of 1.173 at an incremental cost per patient of R$56,839.28, resulting in an ICER per QALY gained of R$48,451.29 and an incremental cost per life-year saved of R$28,266.53. Afatinib led to a QALY gain of 1.165 and increased the cost per patient by R$58,756.87. The ICER per QALY gained was R$ 50,444.25, and the incremental cost per life-year saved was R$29,220.16. Figure 2 presents the results of the DSA for the retrospective study model.

Meta-analysis model

In the meta-analysis model, overall survival was virtually identical for the two strategies. In the arm that received EGFR-TKIs as the first-line treatment, −0.01 life-years were saved in comparison with the
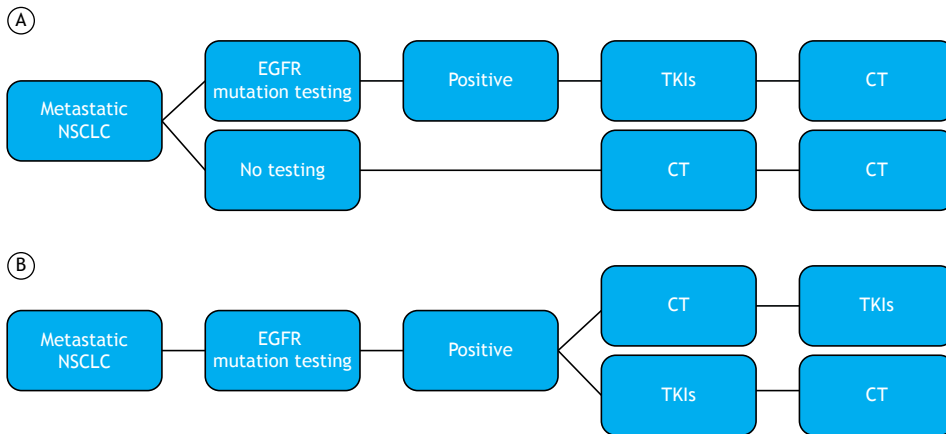

Figure 1. Analytical decision models. In A, retrospective study model. In B, meta-analysis model. NSCLC: non-small cell lung cancer; TKIs: tyrosine kinase inhibitors; and CT: chemotherapy.

Table 1. Deterministic sensitivity analysis parameters.

Parameter	Value considered	Minimum	Maximum
Overall			
Discount on the cost of TKIs	10%	NA	NA
	20%	NA	NA
Gefitinib at a fixed cost	R$1,000	NA	NA
Costs			
Erlotinib	R$5,581.55	NA	NA
Gefitinib	R$2,701.94	NA	NA
Afatinib	R$2,824.43	NA	NA
Monitoring (per cycle)	R$448.72	R$358.98	R$538.46
Supportive therapy (per month)	R$1,034.31	R$827.45	R$1,241.17
Outcomes			
Utility of PFS for TKIs	0.6393	0.6193	0.6593
Utility of PFS for CT	0.6107	0.5907	0.6307
Utility of post-progression survival	0.4734	0.4334	0.5134
Survival			
CI for mPFS for TKIs (retrospective studies)	12.1 months	10.2 months	13.5 months
CI for mOS for TKIs (retrospective studies)	30.9 months	28.2 months	35.7 months
CI for mPFS for CT (retrospective studies)	3.1 months	2.8 months	3.9 months
CI for mOS for CT (retrospective studies)	11.9 months	10.2 months	13.6 months
HR for PFS (meta-analysis)	0.37	0.32	0.42
HR for OS (meta-analysis)	1.01	0.88	1.17

TKIs: tyrosine kinase inhibitors; R$: Brazilian reais; NA: not assessed; PFS: progression-free survival; CT: chemotherapy; CI: confidence interval; mPFS: median progression-free survival; mOS: median overall survival; HR: hazard ratio; and OS: overall survival.

arm that received chemotherapy as the first-line treatment.

Erlotinib led to a QALY gain of 0.193 at a mean incremental cost per patient of R$14,517.13, which resulted in an ICER per QALY gained of R$75,203.26. Gefitinib led to a QALY gain of 0.175 at a mean incremental cost per patient of R$4,741.93, resulting in an ICER per QALY gained of R$27,028.30. Afatinib led to a QALY gain of 0.167 and increased the mean cost per patient by R$5,239.37. The ICER per QALY gained was R$31,352.97. Figure 3 presents the results of the DSA for the meta-analysis model.

DSA

The 95% CI for overall survival (0.009-1.396) was the variable with the greatest influence on QALY. The 95% CI for progression-free survival (30-50%) was the variable with the greatest influence on costs.

Negotiating discounts for the purchase of the target drug or fixing the cost of EGFR-TKIs at a monthly amount of R$1,000.00 resulted in an important improvement in the cost-effectiveness of treatment.

DISCUSSION

The cost of cancer treatment is a growing concern worldwide.[19] The American Society of Clinical Oncology has recently published a framework to assess the value of cancer treatment options on the basis efficacy, adverse events, and cost.[20] Although such initiatives are important and practical, traditional cost-effectiveness models remain essential for estimating the economic implications of cancer treatment options in Brazil. However, in order for cost-effectiveness studies to be considered before health policy decisions are made, such studies should follow some important methodological rules. The most important rule is all relevant costs and benefits to be considered in the study should be identified, assessed, and described in a transparent manner.[21] In addition, it is important to define the clinical context that was considered in the cost-effectiveness study in order to obtain the costs and benefits of treatments and to determine whether that context matches the reality of the locale at which the study will be implemented.[21]

Market movements, government regulations, and tax legislation influence drug costs. Differences in health care systems worldwide make it difficult to translate the results of an economic study into a context different from the one in which that study was developed. Therefore, pharmacoeconomic assessments are relatively specific to the health care system in which they are performed.[21]
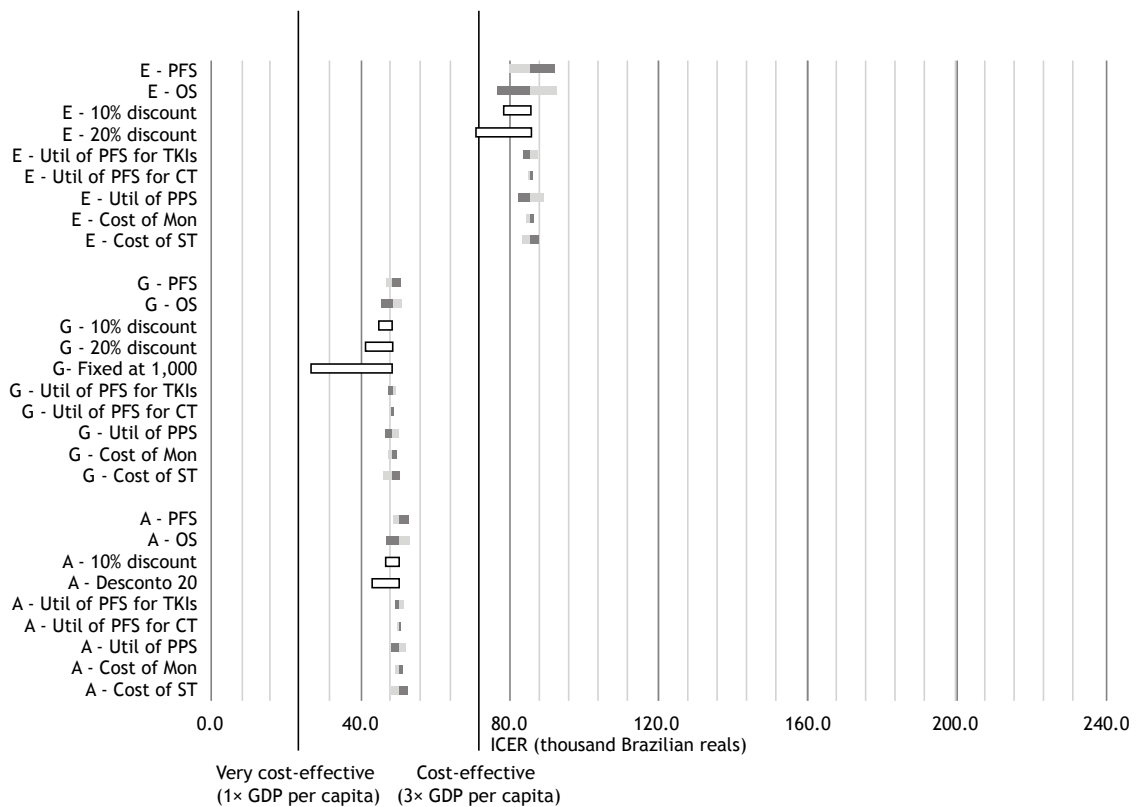

Figure 2. Tornado diagrams for tyrosine kinase inhibitors versus chemotherapy (retrospective studies). E: erlotinib; PFS: progression-free survival; OS: overall survival; Util: utility; TKIs: tyrosine kinase inhibitors; CT: chemotherapy; PPS: post-progression survival; Mon: monitoring; ST: supportive therapy; G: gefitinib; A: afatinib; ICER: incremental cost-effectiveness ratio; and GDP: gross domestic product.

In this light, the major limitation of the present study was the literature used in each model developed. The ideal would be to conduct a randomized prospective study in Brazil comparing EGFR-TKI treatment for *EGFR* mutation-positive patients versus chemotherapy for patients who did not undergo molecular testing. However, a study with such a design would not be approved by a research ethics committee, given that the benefits of molecular targeted therapy are well established.

In our study, each model developed has strong and weak points. In the retrospective study model, the strong points are the overall and progression-free survival values consistent with the literature and the design that is closest to the ideal for the context of the SUS. However, that model was based on two retrospective studies that included two completely distinct populations. Data from the Brazilian population, even retrospective data, could allow an analysis with fewer limitations. Regarding *EGFR* mutation testing, we considered the costs of testing by Sanger sequencing, which has a lower cost than does Next-Gen Sequencing, which is the currently preferred method. In addition, we are aware of the difficulty in making *EGFR* mutation testing available at all SUS facilities throughout Brazil. Centralization of testing facilities can reduce costs and increase

the reliability of test results, whereas regionalized training makes it possible to expedite test results, although at a higher cost and with the challenges of implementing testing at various locations.

In the meta-analysis model, the strong points were the robust data obtained from multiple randomized clinical trials, showing overall and progression-free survival values consistent with those in the literature. However, this model does not reflect the context of the SUS, given that all patients were tested for *EGFR* mutations and approximately 70% of the patients received EGFR-TKIs after chemotherapy failure.

Considering the limitations of each model, we believe that the combination of all findings provides an overview close to the ideal for the context of the SUS. Other studies conducted in Brazil have assessed the cost-effectiveness of using EGFR-TKIs for the treatment of advanced NSCLC. One such study, developed by the Brazilian National Commission for the Incorporation of Technologies into the SUS, discussed the lack of benefit in terms of overall survival and pointed out limitations in performing and funding molecular testing.[22] However, that analysis had severe methodological limitations. Only data from randomized clinical trials were considered, which does not represent the current reality of the SUS,
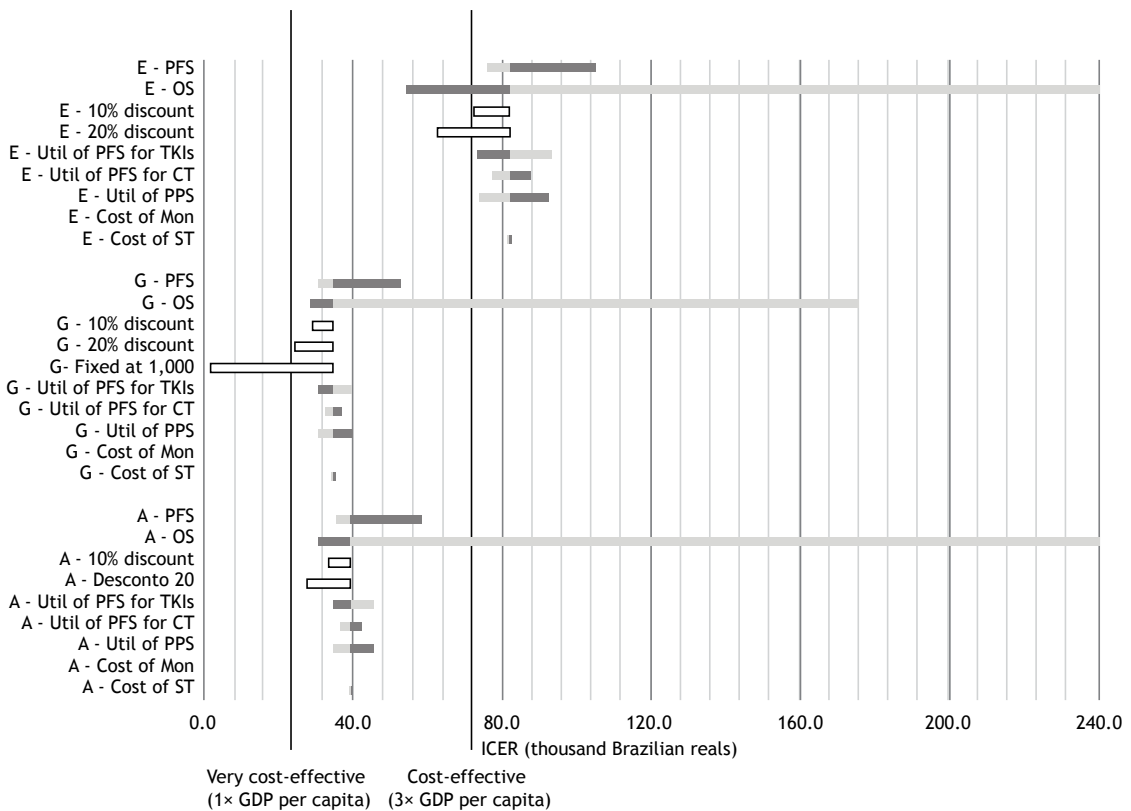

Figure 3. Tornado diagrams for tyrosine kinase inhibitors versus chemotherapy (meta-analysis). E: erlotinib; PFS: progression-free survival; OS: overall survival; Util: utility; TKIs: tyrosine kinase inhibitors; CT: chemotherapy; PPS: post-progression survival; Monit: monitoring; ST: supportive therapy; G: gefitinib; A: afatinib; ICER: incremental cost-effectiveness ratio (ICER); and GDP: gross domestic product.

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given that, within the SUS, tumors are not routinely tested and there is no possibility of patients receiving EGFR-TKIs after chemotherapy failure.

Piha et al.[18] also considered data from randomized clinical trials for assessing efficacy, although information on costs was obtained from the Brazilian Chamber of Drug Market Regulation, causing the costs of platinum-based chemotherapy to be higher than the costs of gefitinib. Therefore, gefitinib surpassed chemotherapy because it had greater efficacy at a lower cost. However, as in the private health care network, the reimbursement for health care services is not based on the cost of treatment within the SUS, although it is fixed at a monthly value of R$1,100.00, a value that was used in our study as the cost of chemotherapy. The exact cost of drugs is not known because each hospital conducts its own negotiations with drug manufacturers so that the cost of treatment is at or below the amount paid by the SUS.

Subsequently, Geib[17] conducted a study of the cost-effectiveness of gefitinib that evaluated not testing for *EGFR* mutations and treating all patients with chemotherapy versus treating *EGFR* mutation-positive patients with gefitinib. Although the design was ideal for the context of the SUS, the author assessed the efficacy of chemotherapy on the basis of retrospective data from his own facility, whereas data on the efficacy of gefitinib were extracted from randomized clinical trials.[17] In addition to the fact that two completely distinct populations were compared, survival is known to be often overestimated in retrospective studies relative to prospective randomized studies. As a consequence, no significant clinical benefit was found, and gefitinib was not considered cost-effective.

Finally, we believe there is no ideal model to address the issue in question within the SUS. However, considering the different scenarios, we can conclude that EGFR-TKIs are cost-effective (EGFR-TKIs have a 64% probability of being cost-effective with an incremental investment of up to three times the GDP per capita of Brazil per patient). Negotiating discounts or fixing costs at an amount lower than that currently paid by the SUS can increase the likelihood of cost-effectiveness to up to 100%. Once such negotiated discounts or fixed costs have been incorporated into clinical practice, another need is molecular testing to inform decisions regarding treatment, which underscores the importance of investing in pathology services within the SUS.

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