BJO
Brazilian Journal of Oncology

ORIGINAL ARTICLES CLINICAL ONCOLOGY

The average cost of treatment according to lung cancer stage using real-world data

Custo médio do tratamento de acordo com o estágio do câncer de pulmão utilizando dados reais

Pedro Aguiar Junior[1,2], Pedro De-Marchi[1], Rafael Paes[1], Isabella Favato[1], Gabriela Monte, Tatiane Montella[1], Filipe Visani[1], Nathalia Afonso[1], Izabella Negreiros[1], Rodrigo Dienstmann[1], Carlos Gil Ferreira[1]

ABSTRACT

Introduction: Immunotherapy led to increased survival in advanced non-small cell lung cancer; however, it has also increased treatment costs. In this study, real-world data was used to evaluate the average cost of treatment of patients with lung cancer. **Material and Methods:** This is a retrospective study that extracted patient-level data from a Brazilian Oncology Group database. The inclusion criteria were patients with non-small cell lung cancer from stage I-IV, and that received at least one line of treatment from 2018 to 2019. The primary endpoint was the average cost of treatment according to the disease stage, and secondary endpoints were the average cost of each line of treatment among patients with advanced disease, and the percentage of this amount that was related to immunotherapy acquisition. The study also assessed overall survival and the cost-effectiveness of immunotherapy at first-line *versus* immunotherapy at second-line or beyond, that was presented as the incremental cost effectiveness ratio per quality-adjusted life years. **Results:** Fifty patients were included, being four (8%) at early-stage (I and II), 10 (20%) at locally advanced disease (III) and 36 (72%) at advanced-stage (IV). The average costs of treatment for each disease stage were respectively US$30,040, US$52,162, and US$95,607 ($p$=0.071). Among patients with advanced disease that received IO, the average cost of the entire treatment was highest with immunotherapy at first line (US$116,623) compared with immunotherapy at second-line (US$112,967) or third-line (US$37,279). Immunotherapy at first-line resulted in an estimated additional 0.26 quality-adjusted life years compared to immunotherapy at second-line (US$19,240). **Conclusion:** The cost of treating non-small cell lung cancer is higher as more advanced is the neoplasm stage at diagnosis. Regarding immunotherapy, the cost of treatment is higher as earlier the treatment is performed, even tough, the cost-effectiveness ratio for first-line treatment seems to be favorable compared to second-line treatment.

Keywords: Lung neoplasms; Cost-benefit analysis; Immunotherapy; Database management systems; Big data.

1. Grupo Oncoclínicas, Rio de Janeiro - RJ - Brazil.
2. Faculdade de Medicina do ABC, Oncologia Clínica - Santo André - SP - Brazil.

Financial support: none to declare.
Conflicts of interest: TDr Aguiar Jr. reported receiving personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Aché Farmaceutica, personal fees from Servier, personal fees from Amgen, and personal fees from Merck Co, outside the submitted work. Dr De Marchi reported receiving grants from AstraZeneca, MSD, Amgen, and Bristol-Myers Squibb and personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Amgen, Merck Co, Bayer, Novartis, MSD, Janssen, Lilly, Takeda, and Sanofi, all outside the submitted work. No other conflicts were reported.
Correspondence author: Pedro Aguiar Junior.
E-mail: pnajpg@hotmail.com

Received on: May 11, 2023 | **Accepted on:** October 26, 2023 | **Published on:** December 29, 2023
DOI: https://doi.org/10.5935/2526-8732.20230419

RESUMO

Introdução: A imunoterapia levou ao aumento da sobrevida no câncer de pulmão avançado de células não pequenas; no entanto, também aumentou os custos do tratamento. Neste estudo, foram utilizados dados do mundo real para avaliar o custo médio do tratamento de pacientes com câncer de pulmão. **Material e Métodos:** Este é um estudo retrospectivo que extraiu dados de pacientes de um banco de dados do Grupo Brasileiro de Oncologia. Os critérios de inclusão foram pacientes com câncer de pulmão de células não pequenas em estágio I-IV, e que receberam pelo menos uma linha de tratamento de 2018 a 2019. O desfecho primário foi o custo médio do tratamento de acordo com o estágio da doença, e os desfechos secundários foram o custo médio de cada linha de tratamento entre pacientes com doença avançada e o percentual desse valor relacionado à aquisição de imunoterapia. O estudo também avaliou a sobrevida global e a relação custo-eficácia da imunoterapia de primeira linha versus imunoterapia de segunda linha ou mais, que foi apresentada como a relação custo-eficácia incremental por anos de vida ajustados pela qualidade. **Resultados:** Foram incluídos 50 pacientes, sendo quatro (8%) em estágio inicial (I e II), 10 (20%) com doença localmente avançada (III) e 36 (72%) em estágio avançado (IV). Os custos médios do tratamento para cada estágio da doença foram respectivamente de US$30.040, US$52.162 e US$95.607 ($p$=0,071). Entre os pacientes com doença avançada que receberam imunoterapia, o custo médio de todo o tratamento foi mais alto com imunoterapia de primeira linha (US$116.623) em comparação com imunoterapia de segunda linha (US$112.967) ou terceira linha (US$37.279). A imunoterapia de primeira linha resultou em um adicional estimado de 0,26 anos de vida ajustados pela qualidade em comparação com imunoterapia de segunda linha (US$19.240). **Conclusão:** O custo do tratamento do câncer de pulmão avançado de células não pequenas é maior quanto mais avançado é o estágio da neoplasia no momento do diagnóstico. Em relação à imunoterapia, o custo do tratamento é mais elevado, pois o tratamento é realizado mais precocemente, embora a relação custo-efetividade do tratamento de primeira linha pareça ser favorável em comparação ao tratamento de segunda linha.

Descritores: Neoplasias pulmonares; Análise custo-benefício; Imunoterapia; Sistemas de Gerenciamento de Banco de Dados; Banco de dados.

INTRODUCTION

Lung cancer is one of the most common neoplasms in Brazil and has a high fatality rate. The Brazilian National Cancer Institute (INCA) estimates about 30,000 new cases annually between 2020 and 2022.[1] In addition, INCA recorded 29,000 deaths from lung cancer in 2019.[2] The severity of the disease can be explained because it affects older patients with comorbidities, in addition to being mostly diagnosed in advanced stages (56-70%) when the 5-year survival rate is less than 10%.[3]

In recent decades, the treatment of advanced non-small cell lung cancer (NSCLC) has greatly improved with the development of targeted therapies and immunotherapy (IO). Population studies have already detected an improvement in patient survival,[4] although at a high and rising costs.[5]

In this context of effectiveness and increasing costs, studies of health technology assessments (HTA) are increasingly necessary. These studies are important to correlate the clinical benefit of new treatments with the respective incremental cost.[6] Classically, health economics studies extract data from randomized clinical trials (RCT) to assess the benefit of a new technology while the costs are calculated according to the context for which the HTA was developed.[7]

Although RCTs are considered strong scientific evidence, the population included in RCTs does not faithfully represent the real-world population due to the strict inclusion criteria of these studies.[8] Furthermore, many ethnic groups present in the Brazilian population are underrepresented in RCTs. Another limitation of RCTs is the lack of data regarding patient's journey through the treatment, as they are studies focused on answering specific questions about the treatment line for which they were developed.

In this sense, there is a growing interest in real-world evidence (RWE) assessing the effectiveness of new technologies in a non-selected population and correlating it with RCT data.[8] In addition, RWE

can provide information about the entire patient journey considering the diversity of therapeutic options available for the treatment of lung cancer today. More recently, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) established RWE as the first trend for health economics studies in the 2022-2023 biennium. In this study, RWE was used to assess the average cost of lung cancer treatment according to disease stage. The purpose of this study is to evaluate the average cost of treating an individual case of lung cancer in a real-world context and the differences in the average amount according to disease stage. Furthermore, this study has the purpose to using real-world data to evaluate lung cancer immunotherapy pharmacoeconomics.

METHODS

Study design

This is a retrospective study that extracted a patient-level data from the *Oncoclinicas* database. *Oncoclinicas* is an oncology group present in 11 out of 27 Brazilian federative units and its database is demographically and geographically diverse. The authors randomly selected the de-identified data from 50 patients. The number of patients included was arbitrarily defined. The inclusion criteria were patients aged ≥18 years, confirmed histological diagnosis of non-small cell lung cancer (NSCLC) and at least one systemic treatment performed at *Oncoclinicas* from 2018 to 2019. The study included patients from stage I to stage IV respecting the Brazilian epidemiological proportion.[9] The start date of the first line was considered the index date. The last follow-up in this study was in July 2021.

All data was de-identified before analysis and the study was approved by the Institutional Review Board with waiver of patient consent (CAAE: 32483720.7.0000.5134). The data lake used in this study does not include clinical and demographic information being focused on clinical outcomes that will be specified in the next section.

Study endpoints

The primary endpoint of the study is the average cost of treatment according to the disease stage. The cost analysis considered only direct costs from antineoplastic drugs acquisition retrieved from the reference table of the Brazilian Drug Market Regulation Chamber assessed in July 2021. All costs were converted from Brazilian Reais to US Dollars using an exchange rate of 5.12. The authors considered the Time to Next Treatment (TTnT) as the treatment duration. The TTnT was established as the time from the first record of the treatment until the last record of the same therapy.

Secondary endpoints were the average cost of each line of treatment among patients with advanced disease, the percentage of this amount that was related to IO acquisition and overall survival (OS), defined as the time from the index date until the last follow-up or death. All patients without a follow-up record were censored in the OS analysis.

Patients with advanced NSCLC that received any approved IO (pembrolizumab or nivolumab or atezolizumab) in monotherapy or combined with chemotherapy were divided into two groups: IO at first-line and IO at second-line or beyond. The authors assessed the TTnT and OS of each group. Finally, the study assessed the cost-effectiveness of IO at first-line *versus* IO at second-line in order to find the best treatment sequencing in terms of RWD pharmacoeconomic.

Statistical analysis

The average costs of treatment according to the disease stage were analyzed through the Kruskal-Wallis test. The average costs of each line of treatment among patients with advanced disease were assessed through the Friedman variance analysis.

The TTnT and OS for IO at first-line *versus* IO at second-line were estimated using the Kaplan-Meier method and compared using the log rank test.

The cost-effectiveness of IO at first-line *versus* IO at second-line was presented as the Incremental Cost Effectiveness Ratio (ICER) per Quality-Adjusted Life Years (QALY). The authors considered four possible health states (alive at first-line, alive at second-line, alive after progression and died) and retrieved each health states' utility from literature.[10] The time expended in each health state was retrieved from the mean survival at the Kaplan Meier curve.

RESULTS

Cost analysis

The study included 4 patients with early-stage NSCLC (stage I and II), 10 patients with locally advanced NSCLC (stage III) and 36 patients with advanced NSCLC (stage IV). The average costs of treatment for each disease stage were respectively US$30,040, US$52,162, and US$95,607 ($p$=0.071).

Considering only patients with advanced NSCLC, the average costs for each treatment line were US$64,927 for first-line, US$54,657 for second-line, and US$20,112 for third-line ($p$=0.115). In terms of IO exposure, the average cost of the entire treatment was US$116,623 among patients treated with IO regimen at first-line, US$112,967 at second-line, US$37,279 at third-line, and US$62,321 among patients that have never received IO, with the IO acquisition cost representing respectively 80%, 75%, 17%, and 0% of all these costs.

Efficacy: TTnT and OS

The median TTnT was 6.9 months for patients treated with IO at first-line and 3.5 months for

patients that did not receive IO at first-line (p=0.073). Considering the TTnT of the first and second-line combined, the median time was 10.6 months for patients treated with IO at first-line and 9.3 months for patients treated with IO at second-line (p=0.643). The median OS were 17.1 months and 18.5 months, respectively (p=0.979).

Cost-effectiveness analysis

The utility estimated for IO at first-line was 1.16 QALY and 0.97 QALY for IO at second-line. The ICER of IO at first-line compared to IO at second-line was US$19,240. The Table 1 summarizes the cost-effectiveness analysis.

Table 1. Real World Drug Acquisition Costs.

	IO at 1st Line	IO at 2nd Line	Utilities
Total Costs	$ 116,623	$ 112,967	-
Mean TTnT 1st Line	12.5 months	4.2 months	0.71
Mean TTnT 2nd Line	2.3 months	6.8 months	0.67
Mean PPS	5.8 months	6.9 months	0.59
QALY	1.16	0.97	
ICER	$ 19,240	Reference	

TTnT: Time to next treatment; PPS: Post-progression survival; QALY: Quality-adjusted life years; ICER: Incremental. Cost-Effectiveness Ratio.

DISCUSSION

The increased cost of anticancer therapies threatens the sustainability of health systems and, consequently, patients' access to the best available treatment. However, a large part of the data regarding the costs of new treatments comes from extrapolation of data from randomized clinical trials that present a population profile that is different from the profile of patients in clinical practice.[11] In other words, costs based on RWD are scarce, especially in the Brazilian literature. These data can support previous estimates and assist in planning future strategies for implementing access to new health technologies.

In this study, it was used a distribution of patients by stage according to national epidemiological data and an evaluation of the average cost per patient treated was performed considering the acquisition of all anticancer therapies throughout the patient's journey. As expected, the average cost per patient was higher as more advanced the cancer stage. In addition, patients diagnosed with advanced NSCLC treated with IO had an even higher average cost compared to patients who did not receive IO.

Although the average cost per patient with advanced NSCLC was high, it was lower than the expected average value considering the standard therapies available in the country. In a study presented at the World Conference on Lung Cancer in 2020, Silveira et al. (2021),[12] estimated the average cost per patient diagnosed with advanced NSCLC at US$142,471 while this study obtained the amount of US$95,607 (-33%).[12] The main hypothesis for this finding is that, due to comorbidities and clinical complications, patients in the real world do not use all available treatment lines, nor do they receive the therapies for the time described in the RCTs that served as the basis for the analysis by Silveira et al. (2021).[12] However, this study has the limitation of not considering patients demographic characteristics, making impossible to compare our population with RCTs populations.

Despite the clinical and demographic differences between patients in this study and patients enrolled in RCTs, considering patients treated with first line IO, it was observed similar clinical outcomes in terms of OS. However, this study was not developed with the specific objective of evaluating the OS of patients and all analyses in this regard require caution.

The limitation regarding the small number of individuals included limits not only the analysis of OS, but of all other outcomes. Furthermore, retrospective studies have statistical limitations that may decrease the accuracy of pharmacoeconomic analyses. The risk of confounding bias from RWD is the most mentioned limitation in the literature and include the clinical practice of selecting patient profiles for certain approaches that would not be chosen randomly, as they would be in RCTs.[13]

Furthermore, even with the improvement of Big Data in the healthcare area and the possibility of collecting and analyzing a large volume of information from different sources, the risk of losing data in a database such as the one used for this study persists.[13] Finally, using TTnT as a measure of exposure to treatments does not allow for the detailing of the dosage administered, nor of the temporary suspensions between cycles. There is also a loss of accuracy of some outcomes inherent to the retrospective design of the study, especially in relation to tumor response and progression-free survival.[13]

A pharmacoeconomic analysis needs to collect and include as much information as possible to reduce uncertainty regarding its outcome. In this sense, the unavailability of data led to the non-inclusion of surgery and radiotherapy costs in the initial cases as well as indirect costs, causing a limitation in this study. In addition, the unavailability of data regarding the occurrence of adverse events represents another limitation for the cost-effectiveness analysis.

Nevertheless, the finding of first-line IO cost-effectiveness of compared to second-line is consistent with other previously published studies that considered RCT data for pharmacoeconomic analysis.[14] The present study is innovative in terms of confirming these findings from local RWD.

CONCLUSION

The cost of treating NSCLC is higher as more advanced is the diagnosis of the neoplasm. Considering only patients diagnosed with advanced NSCLC, the cost is higher when the patient has received immunotherapy, and the cost of acquiring this technology represents a major part of the total cost of patient treatment, regardless of whether the IO is performed in the first or second line. Treatment with first-line IO was cost-effective compared to second-line IO.

AUTHORS' CONTRIBUTIONS

PAJ	Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing
PDM	Conception and design, Final approval of manuscript
RP	Collection and assembly of data, Provision of study materials or patient, Final approval of the manuscript
IF	Final approval of manuscript, Manuscript writing
GM	Final approval of manuscript, Manuscript writing
TM	Conception and design, Final approval of manuscript
FV	Final approval of manuscript, Manuscript writing
NA	Final approval of manuscript, Manuscript writing
IN	Final approval of manuscript, Manuscript writing
RD	Data analysis and interpretation, Provision of study materials or patient, Manuscript writing e Final approval of the manuscript
CGF	Conception and design, Final approval of manuscript

REFERENCES

1. Instituto Nacional do Câncer (INCA). Estimativa 2020 [Internet]. Brasília: INCA; 2019; [access in 2021 Jun 7]. Available from: https://www.inca.gov.br/estimativa
2. Instituto Nacional do Câncer (INCA). Atlas On-Line de Mortalidade [Internet]. Brasília: INCA; 2020; [acess in 2021 Jun 7]. Available from: https://www.inca.gov.br/app/mortalidade
3. National Cancer Institute (NCI). SEER Cancer Stat Facts: Lung and Bronchus Cancer [Internet]. Bethesda: NCI; 2020; [access in 2021 Jun 7]. Available from: https://seer.cancer.gov/statfacts/html/lungb.html
4. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The effect of advances in lung-cancer treatment on population mortality. N Engl J Med. 2020 Aug;383(7):640-9. DOI: http://www.nejm.org/doi/10.1056/NEJMoa1916623
5. Gutierres BS, Aguiar PN, Dourado BB, Alves AL, Matsas S, Simões AR, et al. Evidence strength of pharmaceutical industry-funded clinical trials in metastatic NSCLC: a comparison with other sources of funding. J Thorac Oncol [Internet]. 2020 Jul; [cited 2021 Feb 22]; 15(7):1170-6. Available from: https://pubmed.ncbi.nlm.nih.gov/32217131/
6. Earle CC, Coyle D, Evans WK. Cost-effectiveness analysis in oncology. Ann Oncol [Internet]. 1998; [cited 2017 Mar 21]; 9(5):475-82. Available from: https://academic.oup.com/annonc/article-lookup/doi/10.1023/A:1008292128615
7. Aguiar Junior P, Barreto CMN, Bychkovsky BL, Lopes Junior GL. Cost-effectiveness studies in oncology. In: Araújo RL, Riechelman RP, eds. Methods and Biostatistics in Oncology [Internet]. 1st ed. Cham: Springer; 2018. p. 257-66; [acess in 2021 Jun 7]. Available from: https://link.springer.com/chapter/10.1007%2F978-3-319-71324-3_16
8. Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. JNCI J Natl Cancer Inst. 2017 Nov;109(11):djx187. DOI: https://academic.oup.com/jnci/article/doi/10.1093/jnci/djx187/4157738
9. Mathias C, Prado GF, Mascarenhas E, Ugalde PA, Gelatti ACZ, Carvalho ES, et al. Lung Cancer in Brazil. J Thorac Oncol [Internet]. 2020 Feb; [cited 2021 Jul 11]; 15(2):170-5. Available from: http://www.jto.org/article/S1556086419306586/fulltext
10. Chouaid C, Agulnik J, Goker E, Herder GJM, Lester JF, Vansteenkiste J, et al. Health-related quality of life and utility in patients with advanced non–small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. J Thorac Oncol [Internet]. 2013 Aug; [cited 2021 Jun 8]; 8(8):997-1003. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1556086415334390
11. Aguiar P, Giglio A Del, Perry LA, Penny-Dimri J, Babiker H, Tadokoro H, et al. Cost–effectiveness and budget impact of lung cancer immunotherapy in South America: strategies to improve access. Immunotherapy. 2018 Aug;10(10):887-97. DOI: https://www.futuremedicine.com/doi/10.2217/imt-2017-0183
12. Silveira M, Ferreira CG, Montella T, Carvalho B, De Marchi P. P10.02 A comparison Between the Cost of Lung Cancer Treatment and how much is made Available by Brazilian Government. J Thorac Oncol [Internet]. 2021 Mar; [cited 2021 Jun 8]; 16(Suppl 3):S321. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1556086421005335

13. Bowrin K, Briere JB, Levy P, Millier A, Clay E, Toumi M. Cost-effectiveness analyses using real-world data: an overview of the literature. J Med Econ [Internet]. 2019; [cited 2021 Aug 4]; 22:545-53. Available from: https://pubmed.ncbi.nlm.nih.gov/30816067/

14. Georgieva M, Lima JPSN, Aguiar P, Lopes GL, Haaland B. Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. Lung Cancer [Internet]. 2018 Oct; [cited 2018 Aug 28]; 124:248-54. Available from: https://www.sciencedirect.com/science/article/pii/S016950021830535X#bibl0005