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Practical applications

Barriers in precision medicine implementation among Advanced Nonsquamous Cell Lung Cancer-patients: A Real-World Evidence Scenario

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ABSTRACT

Background

Precision oncology has a prominent role in nonsquamous non-small cell lung cancer (nsNSCLC) treatment progress; however, its access in a real-world scenario might be limited.

Objective

To investigate the time spent in nsNSCLC molecular profile evaluation and its influence on clinical decisions.

Methods

nsNSCLC patients who underwent molecular testing in a private referral Brazilian center between November 2015 and February 2020 were identified. The interval from nsNSCLC diagnosis to the characterization of the molecular profile was determined. Other outcomes, focusing on the biomarker tissue journey, were also assessed.

Results

In this cohort (n = 78), the median time between the advanced nsNSCLC diagnosis and biomarker characterization was 40.5 days (range, 29.5–68.5). The median interval between the diagnosis and the test request was longer than the interval between the request and the results (respectively 29.0 *versus* 12.0 days; $p < 0.001$). At the treatment initiation, 51% (36/71) of the patients who received any systemic therapy did not have their driver mutations panel results available. But on these, 42% (15/36) had a targetable alteration identified later on. Among patients harboring a targetable alteration, only 46% (n = 13/28) received a tyrosine kinase inhibitor (TKI) as first-line therapy. The median time to the TKI initiation was even longer than the median time to all treatment initiation (92.0 *versus* 40.0 days).

Conclusions

Our data show a long median time from advanced nsNSCLC diagnosis and the availability of the biomarker testing in medical practice, which impacted the choice of a non-personalized therapy as the first-line.

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Introduction

Lung cancer ranks as the leading cause of cancer worldwide and accounts for the largest number of cancer deaths (1.8 million deaths, 18.4% of the total). In 2018, approximately 2.1 million diagnoses were estimated, representing 11.6% of the total cancer incidence burden. Of those, 3.27% were observed in South American [1]. Non-small cell lung cancer (NSCLC), which comprises 80–85% of lung malignancies, is the most frequent histology. The knowledge of the tumor molecular pathways as well as the interaction between tumor cells and the immune system led to the development of innovative therapies such as targeted agents and immune checkpoint inhibitors. These therapeutic advances improved the outcomes even for patients diagnosed at advanced stage [2]. Certainly, precision oncology has a prominent role in the remarkable progress in this scenario.

Since targeted therapy use is tailored by molecular findings, such as specific genetic alterations (e.g., EFGR, ALK, ROS-1) and PD-L1 expression, biomarker testing becomes mandatory to guide the therapeutic decisions on the lung cancer approach. In a real-world scenario, there are still many challenges and barriers to be overcome in order to derive the most benefit for the patients. The high cost of such innovative treatments has traditionally been recognized as a major issue. However, the access to the molecular tests is certainly another important matter.

In Brazil, where lung cancer is also among the most common malignancies [3], the health insurances are not obligated to cover other tests for NSCLC apart from EFGR. Thus, the pharmaceutical industry-sponsored programs have been a useful tool to overcome barriers in the molecular testing access, as in other low- and middle-income countries. Regardless of this support, it is well known that the access to molecular testing is limited and data on the frequency of driver mutations are still scarce [4].

Apart from these cost-related factors, issues concerning molecular testing itself such as insufficient tumor samples, inadequate tumor tissue preservation, and logistics delays may impact the prompt identification of a biomarker, which is essential for personalized therapy and may impact the clinical outcomes. The concerns grow since there is evidence suggesting the choice of appropriate targeted treatment in the first-line setting as a determinant of improved clinical outcomes, including best response, quality of life, favorable toxicity profile, and progression-free survival [5–7].

Thus, this study aimed to investigate in a Real-World Evidence scenario (RWE) the use of the NSCLC molecular profile in clinical practice, the impact of the availability of these tests in clinical decisions and to identify not-cost-related barriers to the applicability of the best evidence-based targeted treatment in a Brazilian referral center.

Materials and methods

Study design and cohort

This is a non-interventional, single-center, retrospective study. We included patients with histologically confirmed locally advanced or metastatic nonsquamous NSCLC (nsNSCLC), who underwent molecular testing between November 2015 and February 2020 in a private referral Brazilian center.

Demographic and clinical data were retrospectively collected from medical records. The molecular profile consists of testing alterations such as EGFR, ALK, ROS1, BRAF, and KRAS. For inclusion in this cohort, it was not necessary to perform the tests for all of these genes. The PD-L1 expression was also registered, when available.

Exclusion criteria were as follows: age <18 years, mixed histology (i.e., adenosquamous carcinoma). We also excluded patients with recurrent disease whose biopsy at recurrence was not available, and patients whose data from the biomarker panel conclusion was missing.

The study was approved by an independent Ethics Committee (4.171.310), and the protocols were in accordance with the ethical guidelines of the 1975 Helsinki Declaration. Due to the retrospective nature of this study, the local Human Subjects Committee approved the waiver of participants' free and informed consent.

Endpoints

The primary endpoint was the interval from the diagnosis of advanced nsNSCLC to the characterization of the molecular profile. It comprehends the period between the date of histologic diagnosis or disease recurrence and result of the last biomarker test performed.

The secondary endpoints were the time between the diagnosis or disease recurrence and the testing request, the time between the testing request and the final report, the proportion of patients with confirmed driver mutations before the first-line treatment decision, and the proportion of patients whose treatment changed due to the testing results.

To evaluate the suitability of treatment decisions, the data of drug approvals by the Brazilian National

Table 1. Demographic characteristics.

Variable		Mean/Frequency
Age at diagnosis		69 years (range, 40–92)[a]
ECOG	0	32% (24/76)
(n = 76)	1	59% (45/76)
	2	9% (7/76)
Smoking	Never	51% (38/74)
(n = 74)	Current	12% (9/74)
	Former	37% (27/74)
Gender	Female	51% (40/78)
(n = 78)	Male	49% (38/78)

ECOG, Eastern Cooperative Oncology Group Scale of Performance Status. Data are expressed as absolute numbers (percentage) and median (interquartile range).[a] Number of patients with analyzed outcome/number in whom the information was available.

Health Surveillance Agency (ANVISA) were also taken into consideration.

Given the great variability of techniques available for molecular testing, harboring different performances, and time to results availability, the assays used to evaluate the presence of driver mutations, fusions, and translocations were also investigated. Similarly, different immunohistochemical techniques used to analyze PD-L1 expression were also recorded.

Statistical analysis

Descriptive statistics were used to summarize the data. A normality test (Shapiro–Wilk) was performed for each continuous variable. Categorical data were presented as frequency and percentages, and continuous data were expressed as medians and interquartile ranges. Normality assumed continuous variables were expressed as means and standard deviations. As the study was descriptive, estimation of sample size or statistical power was not applicable.

For comparisons between dependent samples, the Wilcoxon signed-rank test was used. Statistical significance was assumed at $p < 0.05$. Statistical analysis was carried out using SPSS® software, version 20 (SPSS, Chicago, IL).

Results

Patients characteristics

In this cohort, 78 eligible patients were identified. Their demographic, clinical, and histopathological characteristics are summarized in Table 1. The

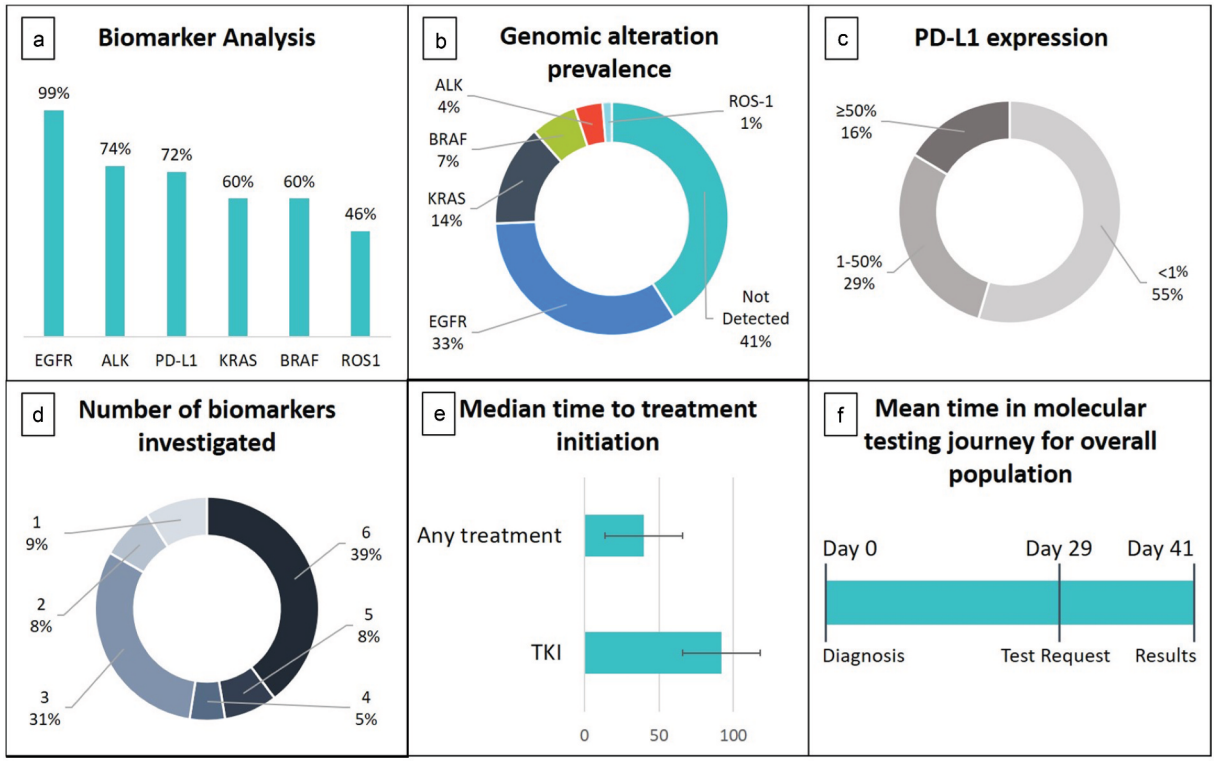

Figure 1. Biomaker analysis of NSCLC, genomic alteration prevalence and time in molecular testing journey of population. (a) Frequency of testing according to the biomarker analyzed, (b) genomic alteration prevalence in the study population, (c) frequency of different categories of PDL-1 expression (i.e., PDL-1 < 1%, 1–49%, ≥50%), (d) number of biomarker tested in the same patient and its frequency, (e) mean time to TKI initiation after EFGR characterization (in days) and mean time for any treatment initiation, (f) mean time spent in the molecular testing journey since the advanced lung cancer diagnosis (in days).

Table 2. Biomolecular assays used in the molecular testing.

Biomarker	Type of test	Frequency
EGFR	rtPCR	39% (30/77)
(*n* = 77)	NGS hotspot	56% (43/77)
	Liquid biopsy	1% (1/77)
	NGS	4% (3/77)
ALK	IHC	93% (54/58)
(*n* = 58)	FISH	5% (3/58)
	NGS	2% (1/58)
PD-L1	22C3	29% (16/56)
(*n* = 56)	SP263	62% (35/58)
	E1L3N	9% (5/58)
ROS1	FISH	97% (35/36)
(*n* = 36)	NGS	3% (1/36)
KRAS	NGS hotspot	96% (45/47)
(*n* = 47)	NGS	4% (2/47)
BRAF	NGS hotspot	96% (45/47)
(*n* = 47)	NGS	4% (2/47)

rtPCR, real time polymerase chain reaction; NGS, next-generation sequencing; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization. Data are expressed as absolute numbers (percentage). Number of patients with analyzed outcome/number in whom the information was available.

mean age at initial diagnosis of was 69 years (range, 40–92). Approximately half of the patients were male (49.0%) and former or current smokers (49%).

Regarding EGFR mutations, it was identified in 26 (33%) patients. Among them, 92.9% (*n* = 24/26), harbored a common sensitizing mutation. Considering the patients whose tumor was tested for ALK translocation (*n* = 58; 74%), this molecular alteration was presented only in three (5%) patients. Likewise, ROS1 fusions were identified in only one patient (2.8%). KRAS and BRAF mutations were evaluated in 47 (60.3%) patients and were detected in 11 and 5 patients, respectively (Figure 1(a-b)).

Considering the patients in which PDL-1 expression was analyzed (*n* = 55), 30 patients (55%) had no PD-L1 expression and only 9 (16%) had a strong expression (>50%) (Figure 1(c)). Of these high expressors, two harbored a concomitant BRAF punctual mutation, while one presented a ROS1 fusion.

Biomarker testing

The majority of the patients (61%) were not tested for the all six biomarkers investigated (Figure 1(d)). There was a great variability of assays used especially for EGFR mutations. Next-Generation Sequencing (NGS) was used only in 4% (three cases). For ALK translocation assessment, almost all cases (93%) used an immunohistochemistry assay. For PD-L1 expression testing, there were three available antibodies, and the most frequent was the Ventana SP263 (63% of all cases). The assays for biomarker testing are summarized in Table 2.

Time for testing results and first line treatment decisions

The median time between the advanced nsNSCLC diagnosis and the final biomarker characterization was 40.5 days (range, 29.5–68.5). With regard to the beginning of the treatment, the median time since diagnosis was 40.0 days (range, 22.3–56.3). Of note, at the treatment initiation 51% (36/71) of the patients did not have their full driver mutations panel results available.

Among the patients whose driver mutation profile was not available at the treatment initiation, 42% (15/36) had a targetable alteration identified later on. Chemotherapy was replaced by a tyrosine kinase inhibitor (TKI) as soon as the molecular profile became available in 67% of the cases (*n* = 8/12). In two patients (17%), the TKI was initiated after disease progression under chemotherapy regimen. Moreover, other two patients started TKI after disease progression and molecular profile characterization, simultaneously.

When assessing all 78 patients, a total of 29 (37%) patients harbored a targetable alteration and just 46% (*n* = 13/28) received a TKI as first-line therapy. Furthermore, the median time to the TKI initiation was more than two times longer than any treatment initiation, 92.0 days (range, 45.0–234.0) *versus* 40.0 days (range, 22.3–56.3) (Figure 1(e)).

Finally, to evaluate in which step of driver mutations characterization a longer time was spent, we compared the median interval between the diagnosis and the testing request to the interval between the testing request and the testing results. We found, respectively, 29.0 *versus* 12.0 days ($p < 0.001$, Wilcoxon signed-rank) (Figure 1(f)).

Discussion

In this study, we found EGFR mutation, ALK translocation, and ROS-1 fusion in a proportion of 33%, 4%, and 1%, respectively. Even in a context of pharmaceutical industry-sponsored tests, many patients (61%) did not have their molecular profile completely characterized. Moreover, at the treatment initiation, EGFR, ALK, ROS1, and PD-L1 results were not available in 51% of the patients. Considering those harboring targetable molecular alteration, 55% did not undergo the targeted therapy upfront, as recommended.

Previous studies have investigated the access to biomarker testing and its rates over time in many countries, including Brazil [8–10]. However, to the best of our knowledge, the present study is the first to focus on the time spent in the molecular characterization and its

impact on treatment choice in a real-world scenario of a middle-income country.

According to The College of American Pathologists (CAP), it should take less than 14 days from the availability of a suitable sample to the report of its final results [11]. In our study, we showed a median of 12 days, which is under this recommendation. Besides, other retrospective studies showed that EGFR analysis lasts from 8 to 17 days in different countries [12].

More recently, a Japanese publication demonstrated a median time of 11 days between the test ordering and its conclusion. The molecular test included EGFR, ALK, ROS1, and PD-L1. Among the patients harboring a targetable mutation, 93% underwent a directed therapy as the first-line [13]. These data contrast with ours. In our analysis, only 52% of the patients had their full driver mutations panel results available at the time of the treatment initiation. It may be explained by logistical challenges that lead to the long interval between the diagnosis procedure and the testing request (median of 29 days).

Awaiting biomarker testing results may delay treatment decisions in patients with advanced NSCLC, which may directly impact their clinical outcomes [14].

This barrier to the personalized medicine implementation might be overcome through the incorporating of reflex NSCLC biomarker testing at the level of the pathologist. Several studies had addressed the role of reflex testing in reducing the time between molecular investigation and treatment initiation. Phung et al. reported a reduction in this interval from 52 to around 23 days in a single-center study [15]. Similarly, a Canadian group demonstrated a shorter interval to the optimal first-line systemic therapy (median, 36 days [IQR, 16–91 days] *versus* 24 days [IQR, 8–43 days], $p = .036$) with the reflex testing utilization [16]. Moreover, according to an institutional review, when EGFR/ALK results were available since the first consultation with the oncologist, nsNSCLC-patients had their time to treatment improved significantly (16 *versus* 29 days, $p = .004$) [14].

Our study also revealed another concern regarding precision medicine incorporation among NSCLC patients in our setting. Although the multiple driver mutations already identified in nsNSCLC, the molecular panel was not complete in a majority of the patients. Most of the panels analyzed tested the different biomarkers concurrently, not sequentially. Even so, the six most important biomarkers were investigated only in 39% of cases. Our data differ from the MYLUNG Consortium, in which 49.0% of the patients were completely tested for these 5 biomarkers, with a tendency of improvement in this rate through the last years [17].

Moreover, in our cohort, less than 4% of the patients had their material evaluated through the NGS method, a technique recognized as fast and accurate. Thus, the use of NGS may also be time-sparing, which contributes to avoiding the initiation of the first-line treatment before the availability of all driver mutations testing results. Our study did not assess ethnic differences in terms of access to NGS testing. A recent study showed that African Americans were less likely to undergo NGS testing when compared to those who are Caucasian (39.8% *versus* 50.1%, $p < 0.0001$) [18].

NGS testing may also improve clinical trial participation, which represents a very important pathway to access innovative therapies. The same study previously cited showed that African Americans were also less likely to be treated in clinical trials (1.9% *versus* 3.9%) due to the lack of access to NGS testing [18].

Our study has some limitations. It was retrospective and performed in a single-center, not reflecting the sociodemographic and genetic diversity of our population. Besides, we considered only the patients whose biomarker tests were requested. Thus, a selection bias could have occurred, since in daily practice many oncologists still use clinical predictors before requesting the tests. Maybe, it could justify the higher rate of EGFR mutations in the studied population (33.3%), comparing to previous publications [4].

As an additional finding, even in a context of pharmaceutical industry-sponsored tests, many patients (61%) did not have their molecular profile completely characterized. Since different biomarkers are tested concurrently, not sequentially, in the panel technique, this data points toward to pre-analytical issues, such as availability of the sample for multiple tests. Additionally, it is known that the molecular alterations analyzed are not necessarily excluding. Thus, the determination of the molecular frequency in our study would be impaired.

Despite the remarkable progress in NSCLC treatment until the mid-2010s, the landscape has been changing rapidly in the recent years. Therefore, the interval of patients recruitment would be considered too long to precisely assess the compliance to the targeted therapy, which is another limitation of this study.

Finally, it is important to mention other important issues related to the personalized therapy applicability, which had important impact in this study. All the advances in this field are accompanied by increasing and often unfordable costs, which limit access to the best oncological care, especially in developing countries such as Brazil, even in the private health system. Indeed, the reality experienced in public health system is even more limited.

Conclusions

In patients with advanced nsNSCLC, our data show a long median time between its diagnosis and the availability of the molecular profile report within medical practice, which may have influenced the choice of a non-personalized therapy as the first-line treatment. Indeed, in this study, the time between diagnosis and testing request was the longest step related to molecular characterization of these tumors. Together, these findings suggest that, even when testing reimbursement is not the main issue, other barriers in precision oncology implementation needed to be faced, such as availability of tumor samples and optimization of the processes involved in testing request, including the multidisciplinary care team training.

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Disclosure statement

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Ethics approval and consent to participate

This study was approved by an independent Ethics Committee (4.171.310), and the protocols were in accordance with the ethical guidelines of the 1975 Helsinki Declaration. Due to the retrospective nature of this study, the local Human Subjects Committee approved the waiver of participants' free and informed consent.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

The authors contributed equally to this work. All authors read and approved the final manuscript.

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