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Molecular Profile of Non-Squamous Non-Small Cell Lung Cancer: A Retrospective Multicentric Study in Lebanon

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ABSTRACT

Introduction: Testing for driver mutations in non-squamous non-small cell lung cancer (NSCLC) before treatment is recommended. Next Generation Sequencing (NGS) allows simultaneous testing of multiple genes. NGS results for NS-NSCLC in Lebanon have not yet been reported.

Materials and Methods: This retrospective multicenter study describes the molecular characteristics of NS-NSCLC in Lebanon. For patients with negative EGFR and ALK tests, NGS results have been collected from the panel companies. Patients' characteristics have been collected from treating physicians.

Results: NGS reports of 40 patients were collected, revealing that 60% had adenocarcinomas, and 80% had metastatic cancer at diagnosis. The most frequent actionable mutations were in the RAS family, accounting for 55%. TP53, STK11, KEAP, and CDKN2A/B were the most common non-actionable mutations. The median OS was 13 months. Patients with actionable mutations had a median OS of 12.5 months, while those with non-actionable mutations had a median OS of 20 months.

Conclusions: This study is the first of its kind to describe the molecular characteristics of NS-NSCLC in Lebanon. NGS seems to be a beneficial test in case of negative EGFR and ALK tests.

Keywords: Ngs; Driver Genes; Lung Cancer; Targeted Therapies; Lebanon

Introduction

Definition and Epidemiology

Lung cancer is defined as a malignant tumor developing within the bronchi or in the lung's parenchyma [1]. With over two million new cases worldwide in 2020, lung cancer ranks second in terms of incidence2. It also accounts for 18 % of all cancer deaths, and therefore is the leading cause of cancer deaths [2].

Histology

Lung cancer is divided into two separate families. SCLC is an aggressive form of lung cancer from neuroendocrine origin [3], whereas NSCLC, the most common subtype accounting for 85 % of all cases and is divided into squamous cell carcinoma and non-squamous (NS) including adenocarcinoma and large cell carcinoma [4]. SCC, among all NSCLCs, has the highest association to tobacco smoking [5]. Despite screening efforts, and its effect on decreasing diagnosis at advanced stages, in most cases, NSCLC is discovered in metastatic setting. [6] When it comes to advanced NSCLC, treatments are not curative. Therefore, palliative systemic therapy or radiation therapy are the standard of care [7]. Since the goal of targeted therapies is to give the patients the drugs that match their specific profile, the standard of care in NS-NSCLC today is to test for mutations that are predictive of treatment response [8]. Therefore, testing for these mutations is an essential part of the management of NSCLC.

Towards Targeted Therapies

Driver genes are genes that, when mutated, lead to cell proliferation. Progress in the field of genetics as well as the sequencing of tumors own DNA, allowed the profiling of tumors DNA. A 2004 study described first the role of EGFR mutations in the response to Gefitinib, a tyrosine kinase inhibitor [9]. This discovery led to a paradigm shift in the management of lung cancer. A similar role of ALK, ROS1 and BRAF V600E mutations has been later on established [10]. Therefore, these mutations should be tested at diagnosis for all patients with advanced NSCLC (category 1). [10] There are other mutations of oncogenic drivers that can be targeted, thus, when EGFR, ALK and ROS1 tests are negative, there is a uniform consensus to screen for RET fusions, HER2 mutations, MET amplification and MET exon 14 mutation10.

Molecular Biology in NS-NSCLC

Mutations occurring in cancers can be classified according to their clinical implications. Actionable biomarkers are mutations that are predictive of response to treatment and therefore of better outcomes. On the other hand, prognostic biomarkers are related to tumor's intrinsic aggressivity and therefore predict survival independently of treatments [11]. Furthermore, agnostic biomarkers predict response to a certain targeted therapy independently of the site [12]. Finally, emerging biomarkers are predictive of response according to several studies, however, are not fully established [11]. While there are many known mutations in NS-NSCLC, only few of them have clinical significance. At the diagnosis of advanced NS-NSCLC, and before any treatment decision, it is important to assess at least the status of EGFR, KRAS ALK, BRAF, METex14, NTRK1/2/3, RET and ROS [11,13]. There is also a uniform consensus that PD-L1 status should be tested upfront. [11] However, patients with both actionable mutations and positive PD-L1 status should be treated first with targeted therapies rather than ICI. [11]

Testing for Mutations

There are two different approaches to test for mutations in NS-NSCLC. The first is sequential testing, where there are different validated biomolecular techniques that can be used, while the other is to upfront test for all known mutations through NGS. A companion diagnostic test, is a test that is FDA approved and recommended to identify biomarkers and mutations that can be targeted by a specific drug [14]. In the past few years, the FDA has approved several companion tests for TKIs in the treatment of NSCLC.

Sequential Testing

Testing for a mutation is a time and resource consuming process. In NS-NSCLC, the presence of certain mutations excludes the possibility of the presence of another one and vice versa. Such mutations are called mutually exclusive mutations. Indeed, KRAS, EGFR, ALK, ERBB2, and BRAF oncogenes are found in more than 50 % of lung adenocarcinomas and up to 90 % of lung adenocarcinomas in Asian never-smokers. However, they are generally mutually exclusive, with the presence of one of them excluding the presence of the others [15]. Sequential testing follows a logical pattern, where looking for the mutations goes from the most to the least frequent mutation in a population, until one of the actionable oncogenes is found. The first tested mutations are EGFR and KRAS using targeted assays.

NGS

NGS, is a technique of massive parallel sequencing that allows to sequence the entire genome or specific regions and genes. Therefore, it allows finding mutations in different chromosomes and genes simultaneously. In the specific frame of NSCLC, the use of NGS allows not only to find mutations of interest, but also Microsatellite instability and Tumor Mutational Burden. In comparison with sequential testing, NGS allows a higher rate of detection of alterations, and is more cost-effective. It has also been linked to better outcomes in terms of quality of life and overall survival [16]. Turnaround time (TAT) is also a major determining factor when comparing sequential testing to upfront NGS. When it comes to sequential testing, either different tests are done simultaneously in the perspective of reducing TAT, or they are done separately to cut costs, however the result should be available within two weeks. In terms of TAT efficacy, upfront NGS is superior to sequential testing, in which 32.5 % of patients exceed the maximum TAT [17]. When it comes to cost, first line parallel sequencing is on average 158 euros cheaper (17%) than sequential testing, on the exception of 45.5 % of patients who have EGFR or KRAS aberrations, discovered only after first line targeted assays17. Although NGS allows obtaining supplementary 0.17 LY and 0.12 QALY, treatments costs are 8 357 euros higher17. Another advantage of parallel sequencing is the need for less tissue material, which is also usually scarce in lung cancers and the higher sensitivity for liquid material.

Insights from the Lebanese Experience

Lebanon is an East-Mediterranean country with an estimated population of 6.8 millions [18]. In additional to classical risk factors such as cigarette smoking and pollution, waterpipe consumption is particularly prevalent, especially in youngsters [19]. Another epidemiological particularity is the widespread of small electrical generators as a surrogate for centrally produced power, with studies showing that people living nearby where at a higher risk for lung cancer [20]. According to the National Cancer Registry, Lung Cancer was in 2016, the second most diagnosed cancer (2nd in males and 3rd in females), with over 1 100 new cases [21]. The average ASR respectively for males and females was 32.1 and 14.3 per 100 000 [22]. From an histological point of view, adenocarcinoma is the most common histology (48%), followed by squamous cell carcinoma (23 %) and small cell carcinoma (13.3%) [23]. It is notable that among MENA countries Lebanon has the highest rate of lung cancer in woman and second highest in men [22]. A paper by Temraz et al. on lung cancer trends in Lebanon reports that cases were 2.5 more frequent in males than

in females and that adenocarcinoma is the dominant histological type in comparison to SCC, thus following a westernized trend [24]. A systematic review from the Middle East and North Africa region including 1215 patients, reported EGFR mutations in 257 of them (21.2%), with the exon 19 deletion being the most common.

It has also reported a higher rate of EGFR mutation in women and non-smokers. [25] The first Lebanese study on driver mutations status in NS-NSCLC, was reported by Fakhruddin et al. on 106 patients with lung adenocarcinoma, with a median age of 62 years old and a 2:1 male to female ratio. In 37.7 % of the cases a KRAS mutation was retrieved, mostly single mutations in the exception of 5 double mutations, with 85 % having a G>T substitution in codon 12 of exon 2. 6 cases had the substitution in codon 13 as well as a case of A>G substitution in codon 61 of exon 3. Men and smokers were at a higher risk for this mutation. The same study retrieved EGFR mutations in 9 cases (8.5 %), and no patient had concomitant EGFR and KRAS mutations. 8 out of 9 of the mutations were exon 19 deletions with one case of L858R substitution in exon 21. It is notable that EGFR mutations were significantly correlated with female sex (p=0.005), non-smokers (p=0.003) and differentiated tumors (p<0.001)26. A single institutional study by Naderi et al from 2015, on 204 NSCLC patients with a mean age of 65.2 years, of which 90 % had NS NSCLC, shows an 11.9 % mutation rate of EGFR27. 25 EGFR mutations were detected in total, since One patient had 2 mutations: an exon 19 deletion and an exon 20 T790M mutation. The frequency of the mutations is a follows : 48% (12) exon 19 deletions, 40% (10) exon 21 L858R mutation, 4% (1) exon 18 G719X mutation, 4% (1) exon 20 insertion and 4% (1) exon 20 T790M mutation27.

Two thirds of the patients in the study that have EGFR mutations were females and non-smokers27. Another 2017 Lebanese study from a different center, by Tfaily et al, included 205 patients, most of them Lebanese, that were tested for EGFR mutations. 32 out of the 205 tested had EGFR mutations. The most detected mutations were an exon 19 deletion in 78.1 % and a exon 21L858R mutation in 21.9 %28. Although the mutation was more frequent in non-smokers and females, the difference was not statistically significant28. ALK status was also studied in 157 patients, out of which only 3 had a translocation (1.9 %)28. Moreover, in a paper by Fakhruddin et al. on 106 cases, both K-RAS and EGFR statuses were studied. 37.7% had a KRAS mutations, of which the majority were male and smokers. On the other side, only 8.5 % had an EGFR mutation.

Materials and Methods

The aim of this paper is to describe the molecular characteristics of NS-NSCLC in Lebanon, when no EGFR, ALK or ROS 1 mutations, are found and to correlate it with survival. This is a retrospective, multicenter study conducted in Lebanon between January and December 2019. The routine practice during that time in the involved institutions was to perform a reflex testing of EGFR mutation and ALK rearrangement for all metastatic NS-NSCLC. Participating centers were asked to provide the NGS reports of their patients with lung cancer. After the exclusion of SCC and SCLC patients, reports information such as the test date, Tumor Mutational Burden, Microsatellite Status, as well as actionable and non-actionable mutations were collected. We then performed a chart review to collect data such as Information on the date of diagnosis as well as metastatic sites at diagnosis, agents used in each line of systemic treatment as well as current status or date of death or lost to follow-up.

Results

The total number of collected NGS reports was 45, from 4 different institutions. After removing 3 patients with SCC and 2 with SCLC, descriptive statistics were conducted on a total of 40 patients. The median age was 65 years old (35-83) and the male to female sex ratio was of 2.4. 60 % had adenocarcinomas and the rest had NOS tumors. 32 patients (80%) had metastatic at diagnosis. 14 had bone metastases, 13 brain and 9 liver metastases.

Concerning NGS findings, the microsatellite status was stable in 73 % of the patients and could not be determined in the 27 % others. Tumor Mutational Burden was low in 38%, intermediate in 33%, high in 4% and unavailable in 20%. NGS retrieved 23 actionable mutations in 55 % of the patients. Figure 1 represents the prevalence of each of these mutations. The most frequent mutations were those in the RAS family, accounting for 55%. Concerning non-actionable mutations, a total of 143 mutations were found, with a median of 4 mutations per patient, Figure 2 is a representation of the number of non-actionable mutations per patient. The most frequent were respectively TP53, STK11, KEAP and CDKN2A/B in 50 %, 28 %, 23% and 20 % of patients.

The average number of lines of treatment was 2. In the first line setting, 25 (63 %) patients received ICI, alone or in combination with chemotherapy, while 13 (33 %) received chemotherapy alone and 2 (5%) received TKIs. Only 17 patients benefited from second line therapies, 8 (47%) received chemotherapy alone, 6 (35 %) received ICIs and 3 (18 %) received TKIs.

Concerning the third line, 7 (47%) patients received ICIs, 5 (33%) chemotherapy alone and 3 (20 %) TKIs. Finally, only six patients received fourth line treatment, divided into three equal groups for chemotherapy alone, ICIs and TKIs. The median OS was found to be 13 months. When divided into two groups, the one with actionable mutations (29 patients) had a median OS of 12.5 months, while the one with non-actionable mutations only (11 patients) had a median OS of 20 months.

Discussion

This is the first multicenter study reporting the characteristics and outcome of patients with NS-NSCLC undergoing molecular testing by NGS technique in Lebanon. It is also, to our knowledge, the first study reporting on the molecular characteristics of NS-NSCLC after

the exclusion of EGFR exon 19 and 20, ALK and ROS1 rearranged tumors. During 2019 and at diagnosis, metastatic NS-NSCLC patients in Lebanon benefitted from a reflex testing sponsored by pharmaceutical companies targeted-essays test for EGFR followed if negative by FISH for ALK and ROS1 rearrangements. It is estimated that EGFR mutations occur in 8.5 to 15.6 % of patients in Lebanese series [26-29] and one series reports ALK rearrangements in 1.9 % of patients [29]. ROS1 rearrangement prevalence has not been reported so far. With this approach, at least 10 - 15% of patients with NSCLC in Lebanon will not need NGS. The purpose of this study was to evaluate the percentage of patients harboring actionable mutations when we exclude the common EGFR, ALK and ROS1 classical mutations usually done as a routine practice in countries with limited resources like Lebanon then to evaluate the capacity to receive potential targeted therapies and to correlate it with survival. Since 2019, Lebanon entered the worst economic crisis of its history, which alongside COVID-19 pandemic, negatively affected the capacity of patients to benefit from cutting edge technologies, such as NGS.

Also, cancer therapies, aside from basic chemotherapy, have been missing repetitively, therefore testing for mutations has been sometimes considered obsolete. The median age of patients (65 years), is concordant to other Lebanese studies on NS-NSCLC [26,27]. The male to female sex ratio of 2.4 is also similar to other reported findings from Lebanon [24,26]. Only one study in Lebanon have reported the rates of KRAS mutations in NSCLC patients, which was 37.7 %26 but in this series all type of KRAS point mutations were included. In our analysis, we found that KRAS G12C accounted for 42 % of the actionable mutations and were found in 25 % of the patients. HER2 mutations, are usually retrieved in up to 4 % of NSCLC, exclusively in adenocarcinomas [30]. In this analysis, it was amplified in two patients and mutated in four, accounting for 10 % of all patients. Met Skip mutations and amplification was found in 8 % of all patients, which is also in a higher percentage than the 1 to 5 % in NSCLC reported in the literature [31].

This high percentage might be explained by the fact that we already excluded around 15% of patients with the common EGFR, ALK and ROS1 mutations.TP53 mutations are usually associated to worse outcomes of radiation and chemotherapy [32]. They are more frequent in SCC than in lung adenocarcinomas and usually found in around 45 % of the patients with adenocarcinomas [33]. In line with the literature, 20 (50%) patients in our series had TP53 mutations. Of note 2 patients were found to have EGFR mutations which were not detected by the PCR technique. This finding was described in other series documenting the false negative rate of EGFR PCR technique, with a sensitivity estimated to be around 70 % depending on the technique [34]. When actionable mutations are found, it is usually recommended that TKIs should be used in first line setting [11]. However, many TKIs have not received FDA approval until recently, with more than 20 TKIs for solid tumors being approved since 2018 [35]. The majority of patients with actionable mutations in our series did not receive the appropriate targeted therapy because of no availability of these drugs via compassionate use programs, non-approval in Lebanon or the non- capacity of buying the drugs from abroad because of the economic crisis. These obstacles make questionable the value of NGS in countries with limited resources.

Moreover, the fact that NGS is not done upfront, and is usually run at a later stage, delays the discovery of actionable mutations, and therefore delays the use of TKI until later stages. Indeed, the gap between the uses of TKIs compared to a combination including ICIs or chemotherapy alone, is wider at first line and becomes smaller until getting even with the others in fourth line. One striking finding in our report is the trend toward better survival of patients with non-actionable mutations in comparison to those with actionable mutations. However no solid conclusion can be drawn because of the retrospective form of our study, the non-comparability between the groups and other confounding factors not taken into consideration such as age, metastatic site, and performance status.Since actionable mutations were found in 23 patients (55%) after the exclusion of EGFR, ALK and ROS1, upfront NGS is a promising approach, and should be considered in Lebanese patients in order to improve outcomes and reduce waiting times before getting the optimal treatment. However, new recommendations should take into consideration the financial hardship for the patients, as well as the limited availability of newly approved drugs in developing countries. Other limitations of the study are that it did not take into account the smoking status, the limited sample size, as well as the descriptive design of the analysis.

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