Driver and actionable mutations in younger patients with lung cancer – are we searching properly?

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Aims. The authors focused on a group of young lung cancer patients with the aim of better understanding the mechanisms of tumor pathogenesis in these patients and search for potential targetable mutations.
Methods. We collected retrospective data on patients under 40 years diagnosed with lung cancer (NSCLC or small-cell lung cancer) from 2011–2020 at the Department of Respiratory Diseases, University Hospital Brno, Czech Republic. Tumor tissue of these patients was analysed by next-generation sequencing (NGS, a panel of 550 variants in 19 genes). Demographic characteristics, smoking history, histology, molecular-genetic results and clinical stage of the disesase were recorded in all eligible patients from accessible medical databases.
Results. Of 17 identified patients in only 8 cases was successful NGS carried out due to lack of sufficient good quality material in the other cases. The most frequently found molecular genetic changes were EGFR, RICTOR and HER2 amplification and MET and FGFR1 amplification. In addition, we found rare pathogenic variants in BRAF and PIK3CA genes. Actionable variants were detected in 75% patients.
Conclusion. We detected very frequent driver and potentially actionable alterations in young patients with lung cancer. This suggests different mechanisms of carcinogenesis in these patients and indicates that they might benefit more from a specific approach than older lung cancer patients.

Key words: lung cancer, young patient, driver, mutation

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INTRODUCTION

The last decade in pneumo-oncology became the era of molecular-genetic testing and personalised anti-cancer treatments arising from this development. This approach together with the newly introduced drugs has led to improved survival outcomes of patients expecially in those with non-small cell lung cancer (NSCLC) (ref.[1]).

In 2017, the Czech Republic ranked 26th in incidence and mortality rate rates of all European countries (incidence 62.3 and mortality 51.6 per 100 000 population, respectively)[2]. The most affected age group was between 65–75 years while patients under 40 years of age accounted for less than 1% of all new cases[2]. There is conflicting data on survival outcomes of younger patients with lung cancer compared to older ones[3-5] as well as on the molecular genetic changes as drivers of carcinogenesis in this population[6-11]. The current investigation was on young patients with lung cancer whom we previously reported to have significantly worse survival than older age groups[12].

In clinical practice in the Czech Republic, samples of patients with NSCLC histology are routinely tested for the mutational status of the epidermal growth factor receptor (EGFR), translocation of anaplastic lymphoma kinase (ALK) and ROS-1 rearrangements and expression of programmed death-ligand 1 (PD-L1). Other molecular-genetic changes (NTRK, MET, RET, KRAS, and others) may be examined on reasonable physician request[13]. Sufficient and high-quality samples of the tumor tissue are needed as pathologists have to have enough material for molecular-genetic analyses where immunohistochemistry (IHC), fluorescence in-situ hybridization (FISH), real-time PCR assays and other methods are used. This also increases the demand on size and number of the biological specimens used for testing. The next-generation sequencing (NGS) uses targeted sequencing panels enabling us to analyze multiple genetic changes from one small tissue sample at one time[14,15]. Even though NGS is not used in all patients in common clinical practice due to its time-consuming nature and high costs, it is expected to become a standard practice, at least in some types of patients with cancer (young adults, patients with hereditary forms of cancer etc.)

Several studies on tumor pathogenesis of lung cancer in young patients have been performed. According to one large American study by Sacher et al. from 2002–2014, patients with lung cancer aged under 50 years had 59% likelihood of having a targetable genotype that was

significantly more frequent than older lung cancer patients[7]. Similar results were reported in a recent study on a Chinese population by Yang et al.[8] and in further Asian studies. In contrast to numerous examinations of molecular changes in young patients with NSCLC Asian populations, there is a paucity of comparable data from European countries[6,16].

Our study focused on a group of young patients (under 40 years) who had been diagnosed with lung cancer over the last 10 years at the Department of Respiratory Diseases (part of Comprehensive Cancer Center), University Hospital Brno, Czech Republic. Tumor tissue of these patients was subject to next-generation sequencing (NGS) in order to better understand the mechanisms of tumor pathogenesis of lung cancer in younger people and to assess the percentage of targetable mutations in these patients. We hypothesized that in the cancer genomes of younger patients with lung cancer highly prevalent are driver mutations a high percentage of witch are therapeutically targetable.

MATERIALS AND METHODS

We retrospectively searched for patients younger than 40 years and diagnosed with lung cancer from January 2011 to February 2020 at the Department of Respiratory Diseases, University Hospital Brno. For this purpose, reports from the National Oncology Registry of the Czech Republic and medical databases of the University Hospital Brno were used. In all eligible patients demographic characteristics, smoking history, histology, molecular-genetic results and clinical stage of the disesase were recorded from the accessible medical databases.

Inclusion criteria

Age under 40 years at the time of diagnosis, histologically confirmed diagnosis of lung cancer (NSCLC or small-cell lung cancer), availability of histological sample, acceptable size and quality of the sample, patient‘s signed consent to molecular-genetic examination.

Preparation of a sample and NGS method

A technology used for NGS sequening was GeneReader NGS and a sequening panel QIAact Lung DNA Panel. This panel is able to examine 550 variants in 19 genes known to be involved in lung cancer pathogenesis and potenially targetable by avaliable cancer drugs. The list of gene panel is avaliable in Supplemetary material. Results of NGS testing were evaluated by molecular geneticist to provide biological interpretation of the identified mutations and consulted by the team to evaluate the clinical significance.

Ethics

The study was approved by the Institutional Ethics Committee of the University Hospital Brno, date of approval: April 27th, 2020, reference number: 25-270420/EK. All patients gave consent to molecular-genetic testing of their tumor tissue for scientific purposes.

RESULTS

We identified 17 patients with lung cancer aged under 40 years. Mean age of the cohort was 33.1 years, 10 were males and 7 females, Caucasian race dominated. Twelve patients were smokers or former smokers. The most common histological cancer type was adenocarcinoma, other histology was rare. Sixteen patients were diagnosed with

Table 1. Patients with lung cancer under 40ty diagnosed in years 2011–2020.

Number of sample	Gender (M/F)	Age (years)	Race	Smoking (Y/N)	Histology	Standard analysis	Clinical stage
1	F	35	C	Y	pleomorphic ca	not tested	IVb
2	F	37	C	Y	adenocarcinoma	EGFR-	IIIB
3	F	24	C	Y	adenocarcinoma	EGFR-, ALK-	IVb
4	M	35	C	N	adenocarcinoma	EGFR-, **ALK+**	IVb
5	M	38	C	N	adenocarcinoma	EGFR-, **ALK+**	IIIB
6	F	25	C	Y	adenocarcinoma	EGFR-, ALK-, ROS1-	IVb
7	F	22	M	Y	mucoepidermoid ca	EGFR-, ALK-	IVa
8	M	21	C	Y	large cell carcinoma	EGFR-, **ALK+**	IVb
9	M	40	C	Y	adenocarcinoma	EGFR-, ALK-	IVa
10	M	38	C	Y	sqaumous carcinoma	not tested	IIIA
11	M	39	C	N	adenocarcinoma	EGFR-, ALK-	IVb
12	M	39	C	N	adenocarcinoma	**EGFR+**	IVb
13	M	31	C	Y	mucoepidermoid ca	not tested	IB
14	M	23	C	Y	adenosquamous ca	EGFR-, ALK-	IVb
15	F	39	C	Y	adenocarcinoma	EGFR-, ALK-, ROS1-	IVb
16	F	39	C	Y	small cell lung cancer	not tested	IIIB
17	M	38	C	N	adenocarcinoma	EGFR-, ALK-	IVa

M, Male; F, Female; C, Caucasian; M, Mongoloid; Y, yes; N, no; bolt, positive result.

locally advanced or metastatic clinical stage of the disease. Basic molecular-genetic examination revealed the presence of EGFR mutation in one patient (deletion on exon 19) while ALK rearrangement was detected in 3 cases. All characteristics are presented in Table 1.

Of the 17 patients´ original tumor tissue samples, 11 patients had remaining histology samples after the basic molecular-genetic examinations. The other 6 patients had no additional histological material for further molecular-genenetic analysis. Three samples did not pass the quality control and were excluded. The remaining 8 tissue samples were analyzed by the NGS method.

The most frequently observed molecular genetic changes were copy number variations (CNVs): EGFR amplification (5 cases), RICTOR amplification (3 cases), HER2 amplification (2 cases) and further MET amplification and FGFR1 amplification in one case. In addition, we found rare pathogenic variants in BRAF and PIK3CA genes. In one case, rare activation mutation in exon 18 of EGFR gene was discovered that is not commonly covered by commercial PCR assays. Actionable variants were detected in 6 out of the 8 tested patients (75%). In two patients, there was more than one targetable change. NGS results are summarized in Table 2.

DISCUSSION

Although lung cancer is a rare disease in younger patients, it deserves major attention especially due to its poor prognosis[4,5,7,12]. More than 60% of young patients with NSCLC are diagnosed in an advanced clinical stage[3-5,12]. Some authors report that up to of 80% patients are diagnosed in clinical stage IV (ref.[3,12]). This specific group of patients is presumed to have different machanisms of cancerogenesis compared to older patients with lung cancer. Unfortunately, the commonly tested predictive markers in lung cancer give only partial insight into these mechanisms. There are several aspects and conflicting points in relation to this group of patients.

a) Definition of a "young" patient with lung cancer

There is no consensus on age limit for a "young patient" in pneumo-oncology. Some focus on the very low age group (< 20 years)[16] while others set the borderline at around 50 years of age[7,17]. In the age group < 20 years, the diagnosis of lung cancer is extremely rare. On the other hand, patients aged around 50 years usually have a longer smoking history and the pathogenesis of their disease is similar to older patients. In our study, we chose patients younger than 40 years for inclusion. This is in accordance with published reports[3,6-8,12].

b) Heterogeneity of histological types

Another problematic issue is the histological heterogeneity of this group. In our NSCLC patients, adenocarcinomas dominated[3,6,7,12]. Some published only to this histological subtype[9,10] however other studies include other histologies (squamous, large cell carcinoma)[8]. Polish authors reported a group of young patients with a high proportion of small cell lung cancer (SCLC) (ref.[16]). This abnormally high proportion of SCLC histology in young Polish patients can be explained by geography as data comes from three large industrial cities in Poland.

c) Smoking habits

Smoking is still considered the crucial factor for carcinogenesis in lung cancer[18]. Tobacco comsumption is attributable to 91% of lung cancer cases in men and 69% in women[18] while DNA methylation seems to be one of the potential mechanisms of cancerogenesis of lung tumors[19,20]. There is also a difference between smokers and neversmokers and a correlation between the number of pack-years and the extent of DNA methylation

Table 2. Results of NGS of eight analysed patients under 40 years of age.

Number of sample	Histology	Standard testing	Tumor cells (%)	NGS results
7	mucoepidermoid carcinoma	EGFR-, ALK-	90	**HER2 amp.**
10	squamous carcinoma	not tested	70	EGFR amp.
11	adenocarcinoma	EGFR-, ALK-	95	**BRAF p.G466V,** EGFR amp., **MET amp.**
13	mucoepidermoid carcinoma	not tested	80	**RICTOR amp.**, EGFR amp.
14	adenosquamous carcinoma	EGFR-, ALK-	30	EGFR amp
15	adenocarcinoma	EGFR-, ALK-, ROS1-	80	**PIK3CA p.G545L**
16	small cell lung cancer	not tested	80	**HER2 amp., FGFR1 amp., RICTOR amp.**
17	adenocarcinoma	EGFR-, ALK-, ROS1-	90	**EGFR del. c.2127_2129delAAC (exon 18),** EGFR amp., **RICTOR amp.**

Bold, potentially actionable mutations.

changes[19,20]. According to Hirao at al., the risk of loss of heterozygosity in chromosome 3 (3p 21 LOH) increases with tobacco pack-years, and the phenomenon is more prevalent in individuals who started to smoke in an early age[21]. Similarly, in another study, higher tumor mutation burden (TMB) was associated with higher age and longer smoking history[22] All these findings support the hypothesis that lung cancer in younger age may have different mechanisms of pathogenesis to older patients with lung cancer.

d) Interracial and interethnic variability

Differeces in incidence of EGFR mutations between Asian and Caucasian populations are well documented[23,24]. However, further research demonstrated that significant variability in EGFR incidence exists even among individual ethnic groups of Asian populations[25]. Along with gender and smoking status, a link between region and ethnicity and incidence of EGFR mutations was found (Vientnamese 64.2% vs Indian 21.9%) (ref.[25]). Similar variations in incidence were found in ethnic groups across Latin America for EGFR and KRAS driver mutations[26]. Finally, Dearden at al. reported significantly higher incidence of EGFR positivity in Asian population while KRAS mutation was more frequent in Western populations[27].

e) Variability of molecular-genetic data

Several previous studies focused on molecular-genetic patterns, however, the data are not consistent. Only a few old studies used NGS for detection of all pathological genome changes in young patients with lung cancer[6,9,11]. In the majority, only selected drivers of oncogenesis were studied[7,8,10] while only one team reported analyses of the germinal genome[11]. To date, there is no international consensus on standardized method and panel of molecular-genetic analysis for patients with lung cancer.

Results of molecular-genetic testing

Molecular-gentic testing is mainly perfomed in NSCLC. The majority of studies on molecular-genetic changes in young patients with NSCLC have been conducted on East Asian populations[8-10,11] while similar reports on European or American cohorts are sparse[6,7,16]. Yang et al. reported significantly higher rates of molecular genetic changes in young patients with lung cancer (68.5% vs 54.8%, P=0.05) (ref.[8]). Translocations in paticular were more common compared to older subjects (22.2% vs 4.1%, P<0.001) (ref.[8]). According to Hou et al., almost 80.5% of young patients with adenocarcimas harboured targetable mutations compared to 54% in the older age subgroup[9]. Abberant pathways of NTRK/KRAS/PIK3CA and p53 were highly prevalent in young patients with NSCLC (ref.[11]). While the relatively frequent ALK mutation in young NSCLC patients is strongly supported by evidence[9,11,28], the rates of EGFR positivity in NSCLC of young patients are unclear[9,10,29,30]. KRAS mutation is less common in young patients.

Some Asian studies on young patients with NSCLC focused mainly on adenocarcinoma histology, predominantly in never-smokers[9-11]. The following molecular-genetic changes were detected in young Asians: EGFR mutations (21.3% to 56%), ERBB2 mutations (24.7%), EML4-ALK translocation (from 16.1% to 16.9%), TP53 mutations (from 9% to 27.7%), KRAS mutations (from 3.4% to 11.1%), BRAF mutations (3.4%), and a number rare mutations, including PIK3CA (1.1%), HER2 (1.1%), ROS1 (1.1%), RET (1.1%), CDKN2A (1.1%) and CTNNB1 (1.1%) (ref.[9,10,11]). In our study, the most frequently altered gene in NSCLC/SCLC was EGFR, which was, in agreement with the Asian studies, mutated in 50% of cases; the second most frequent aberration was RICTOR amp. and HER2 amp., which had 25% prevalence, similarly to previous studies. In addition, we observed one rare mutation in BRAF and PIK3CA.

Studies performed on Caucasian populations are sparse and the data are somewhat incomplete. In an Italian study (the only European one), the authors examined 26 young patients with lung adenocarcinoma and reported only 3 main pathogenic mutations (TP53, EGFR, KRAS) (ref.[6]). In a large American study, samples of 1,325 patients with NSCLC were tested for the 5 main targetable mutations (EGFR, ALK, HER2, ROS1 and BRAF) (ref.[7]). The authors concluded that younger age was associated with an increased frequency of a targetable genotype as patients diagnosed at age 50 years or less had an increased likelihood of harboring a targetable genotype. Of the analyzed mutations, EGFR, ALK, HER2 and ROS1 were associated with younger age[7]. Neither of these 2 studies used NGS as the method of genetic testing.

Limitations of the study

The main limitations of this study are small sample size, its retrospective nature and the lack of a comparable control group. Another factor is that standard testing (EGFR, ALK, ROS1) was not carried out on all patients for histological reasons. NGS sequencing was performed only at the DNA level and therefore we have no information on the presence of ALK and ROS1 gene rearrangements in some patients (see Table 1,2). The lack of biological material did not allow us to complete these analyses.

Future studies

In this pilot study, we demonstrated that 6 out of the 8 young patients with lung cancer harboured potentially targetable mutations in their cancer genomes. Genetic mutations observed in this young adult age category were different to those reported from older age groups. We anticipate a prospective study in the future with NGS analyses of tumor samples of under-40 patients with lung cancer. Beyond better understanding of the molecular pathology in this age category, the results would open a path towards personalized medicine for these patients.

CONCLUSION

Our data show that young patients with lung cancer harbour different tumor-driver genetic alterations com-

pared to older age groups. This suggests different mechanisms of carcinogenesis in younger patients with lung cancer. Further studies are needed for better understanding of this issue.

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