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Prognostic Intake of Molecular Markers in Lung Cancer The Pulmonologist Point Of View

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ABSTRACT
Lung cancer remains one of the most frequent pathologies in Pulmonology Departments. Tumor extension, histopathological types, and treatment influence the prognosis and survival in lung cancer. Five years survival dramatically decreases for the 4th-stage of the disease. Non-small cell lung cancer (NSCLC) represents the vast majority of lung cancers. In the last decades, important findings have been made on identifying standardized molecular biomarkers that control tumor growth in lung adenocarcinoma. The discovery of new drugs led to the increased survival, even in extensive forms of the disease. The greatest advances could be obtained by targeting EGFR genetic mutations or EML4-ALK translocate in patients diagnosed with adenocarcinoma lung cancer.

Keywords: lung cancer, TNM stage, molecular markers

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Lung cancer remains one of the most frequent pathologies in Pulmonology Departments. All international statistics report lung cancer as the most important cause of mortality. The 5-year survival rate is one of the smallest comparing to other cancers of pancreas, esophagus, liver, and stomach [1,2]. Also, lung cancer is a leading type of metastatic cancer [2].

Pulmonologist clinical experience confirms the epidemiological data regarding the bad prognosis of lung cancer, over half of the patients is diagnosed with locally advanced or invasive metastatic lung cancers [2]. Primary objectives of care are to prolong the survival time and to maintain a good quality of life as long as possible.

In the last two decades, a lot of progress was done, especially, in the field of oncologic treatment and personalized management of each case gained interest against of conventional chemotherapeutic treatment. One of the main interests of the multidisciplinary team is to establish a rapid and correct diagnosis and treatment options with minimum side effects. Pulmonologist, pathologist, oncologist, thoracic surgeon, radiologist, and nuclear medicine specialist are equally involved [3].

Survival in lung cancer is dependent on histologic subtype, anatomic tumor extension revealed by the TNM stage, gender, age, performance status, comorbidities, genomics, environment and treatment-related factors [4].

TNM staging is important in predicting the rate of recurrence and survival. The 8th edition of the Union for International Cancer Control TNM Classification of Malignant Tumors was recently updated. Five years of survival for extended tumor or IV-stage NSCLC disease is limited to 5-13% [4,5].

Therapy in lung cancer is established according to histological type [non-small cell lung cancer (NSCLC) represents 80 to 85% of all lung cancers], TNM stage and, lately, by the presence/absence of driver mutations, making possible new personalized therapy, capable to predict a better patient's therapeutic response and to aim mostly malignant cells with minor side effects [4,6]. As the first presentation of a patient in a Romanian Pneumology department, specialists need to be aware of the real possibilities of improving prognosis by earlier detection of molecular markers.

Once the TNM stage and histologic type of lung cancer are precisely defined, it is recommended the identification of available molecular markers which could influence the treatment options and a better quality of life.

The available molecular markers in Romania are [7,8]:

- EGFR (epidermal growth factor receptor) - ~18% more frequent at Asian patients;
- ALK-1 (the anaplastic lymphoma kinase) - ~ 2%;
- ROS1- ~ less than 1%;
- In case of recurrence or tumor progression in patients treated with EGFR tyrosine-kinase inhibitor (EGFR TKIs), the T790M resistance mutation for EGFR is indicated to perform.

Nowadays, molecular testing can be performed on [6,7]:

- All patients with locally advanced or metastatic stage adenocarcinoma, no matter of race, gender, smoking history or other clinical risk factors,

- Mixed cell lung cancers but with an adenocarcinoma component, no matter of histological grade

- Selected patients with squamous NSCLC, for example, those with a light or never smoking history.

It is recommended to test, at the moment of initial diagnosis, all patients presenting lung adenocarcinoma in advanced-stage disease (stage IIIB, IV) who are candidates of bad evolution or progression, but are suitable for therapy and also patients, previously diagnosed with a resectable-stage disease, but with recurrence of disease [6].

Molecular diagnosis is based on biopsy of solid lung tumor tissue and if sufficient tissue is not available, the liquid biopsy could be done. "Liquid" biopsy is a blood based test which identifies tumor DNA (ctDNA) for EGFR mutation. The more advanced disease is, characteristics are predictive for a positive result [9].

There are some discussions about molecular markers indication in patients with early stages [I and II stage] of NSCLC. For these resectable stages, the treatment has curative intent using surgery, chemotherapy, radiation therapy or a combined modality approach.

According to 2nd ESMO Consensus Conference about NSCLC, the choice of adjuvant therapy should not rely on molecular analyses in the early stages (I and II). It is known that there is a high-risk subset that develops recurrence of lung cancer, despite the early stage of disease. Molecular markers may identify patients who are at higher risk of relapsing who therefore may be more likely to benefit from targeted chemotherapy [10,11].

The last UpToDate include molecular markers as prognostic factor placed near histology (including tumor cells in regional lymph nodes), tumor grade and comorbidities [11].

American guidelines encourage testing for EGFR mutations or ALK rearrangement in patients with newly diagnosed localized NSCLC [12]. However, there is no evidence to indicate molecular marker testing at the time of the initial diagnosis for localized NSCLC. Such testing is optimally performed on tissue obtained when a recurrence occurs if original tissue sample missed. Currently, there are ongoing several clinical studies with the indication of targeted agents as an adjuvant therapy for stage 1 and II NSCLC [6,10].

Recognized EGFR mutation is essential because it is a significant predictor of response to EGFR TKIs. Female gender, younger age, Asian

ethnicity, never smokers or smokers are frequent characteristics identified in carriers of positive EGFR driver mutation [10]. The presence of a driver mutation is associated with improved median progression free survival time under EGFR TKIs treatment and a good quality of life.

In Romania, there are three EGFR-TKIs available for patients with NSCLC according to the National Protocols. Erlotinib, Afatinib, and Gefitinibum are indicated in patients older than 18 years, as a first line, maintenance or second-line treatment in patients with lung adenocarcinoma, locally advanced or metastatic disease (stage IIIB or IV), having EGFR activating mutations [7].

The clinical trial ML20650 (EURTAC) closed in April 2012, shows a progression-free survival of 10.4 months using Erlotinib towards chemotherapy with a median PFS of 5,1 months. In the clinical trial (IPASS Study), was shown that patients with positive EGFR respond better to TKI therapy than standard chemotherapy, and the probability of PFS is increased by using Gefitinibum vs. Carboplatin/ paclitaxel comparative to EGFR negative mutation [7,10]. The exclusion or interruption criteria represent the presence/ occurrence of the T790M point mutation of EGFR or the occurrence of other secondary adverse events as acute interstitial lung disease [7,10].

In the presence of the T790 mutation, Osimertinib doubles the PFS time versus chemotherapy with Platinum-pemetrexed (10.1 vs. 4.4 months) [13].

Presence of ALK in NSCLC represents 4% of NSCLC adenocarcinoma in the US and 2% in Israel, occurring more frequently in nonsmokers and younger patients. It predicts for sensitivity to ALK-TKIs (Crizotinib, Alectinib, Ceritinib) and significantly prolongs progression-free survival compared to chemotherapy (7.7 vs. 3 months) [10].

In conclusion, adding the molecular markers in the management of NSCLC, an improvement of the prognosis of patients will get, especially, in locally advanced and metastatic stages of lung adenocarcinoma.

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