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Review Article

Clinical Implications of Early Molecular Diagnosis in Lung Cancer- brief review

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Introduction

Lung cancer is a major issue in oncology pathology worldwide. According to the WHO, this disease is the number one cause of death in both men and women worldwide [1]. Worldwide The countries with the highest incidence of lung cancer meet in Polynesia and Hungary [2]. in Europe in 2018 According to the data provided by GLOBOCAN, the incidence of lung cancer was 470,039 new cases, of which 311,843 men and 158 196 women [3]. The highest incidence was in Hungary, Austria, Germany, Slovenia, Latvia, Romania, the last places being Portugal, Malta, Lichtenstein [4]. For the correct analysis of the survival rate of patients diagnosed with lung cancer, the tumor stage (microcellular lung cancer and non-microcellular lung cancer) were considered; histopathological type (adenocarcinoma, squamous cell carcinoma, neuroendocrine lung tumors - small cell carcinoma, carcinoid; type of treatment (surgical, surgery-chemotherapy, surgery-radiotherapy, surgery-chemo-radiotherapy) [5]. Advanced lung cancer has an extremely poor prognosis, with a 5-year survival of only 5% [6]. An early diagnosis of lung cancer is needed to increase survival. A rapid personalized diagnosis (molecular, imaging, anatomopathological, immunohistochemical) is required in order to initiate an early personalized treatment [7]. After establishing the personalized diagnosis, the therapeutic attitude in the case of lung cancer the treatment can be started [8]. In this context, Molecular diagnosis of lung cancer can be made in the early stages of the disease.

The authors have a significant research activity in the early detection of tumor markers and the development of stochastic sensors. They participated in research projects: 2014 - 2017 PN II, 22/2014, Multimode Microsensors based on micro and nano-structural materials with applications in biomedical

analysis; 2018 - in progress - Program 4 - Fundamental and Frontier Research - "Complex Border Research Projects - PCCF type" project number PN-III-P4-ID-PCCF-2016-0006, in Romania. Latest publication in the field - A Screening Test for Early Diagnosis of Microcellular Bronchopulmonary Cancer-Pilot Study; Claudiu-Eduard Nistor, Raluca-Ioana Stefan-van Staden, Adrian Vasile Dumitru and Camelia Stanciu Gavan; Journal of Clinical Medicine; J. Clin. Med. 2020, 9, 76; two:10.3390/jcm9010076 [9].

Profiles of serum tumor markers for lung cancer groups

Examination of tumor markers in the blood is much more affordable and more easily accepted by patients. These examinations are very useful to doctors for patients with suspected lung cancer. Early personalized diagnosis plays a very important role in early personalized treatment. The onset of personalized treatment differs depending on the histopathological type of the tumor. Thus, for some tumors the therapeutic regimen begins with surgical treatment, while other tumors begin with chemotherapy. Therapeutic efficacy is followed serologically much more easily than imaging follow-up.

Profile of serum tumor markers for adenocarcinoma: CYFRA 21-1, CEA, P53, cytokeratin 19 (CK19).

CYFRA 21-1 [cytokeratin fragment 19 (CK19)] is found in almost all of the lung adenocarcinomas have been tested and has more sensitivity and specificity compared to other biomarkers [10]. Cytokeratins, in particular fragment 19, is an epithelial tissue protein, considered to be an ideal candidate for the detection of carcinoma [10-12]. The normal serum level of cytokeratingin 19 is about 3.3 ng / ml [13,14].



CEA is not a specific tumor marker for lung cancer, but together with other markers it can provide informations. There has been a higher increase in serum levels in Non-small cell lung cancer (NSCLC) [10,15]. Normal EAA values are 3.8 ng / ml [10].

The mutation of the TP53 tumor suppressor gene occurs in Non-small cell lung cancer in 34% of smokers patients with NSCLC [16]. The presence of this protein suggests resistance to chemotherapy [17]. TP53 detection is realised by FISH technique [18].

Profile of serum tumor markers for squamous cell carcinoma: CYFRA 21-1, squamous cell carcinoma-associated antigen (SCC) and Thioredoxin (Trx).

CYFRA 21-1 in the literature of speciality is specified to be the highest values together with levels of CEA with serum squamous cell carcinoma (SCCA) which characterizes the squamous lung cancer [19].

SCCA - squamous cell carcinoma-associated antigen - is protease serum inhibitors, is associated with the emergence and development of squamous cell carcinoma. It has very high values and is closely related to the prognosis of squamous lung cancer. [20]. The presence of the SCCA marker at the onset of the disease may suggest the diagnosis [21].

Thioredoxin (Trx) - is a protein that is very important in the redox process related to the lung tumor, in the peripheral blood under oxidative stress conditions [22]. The presence of this marker is interpreted alongside of SCCA, CYFRA21-1 and CEA [19].

Profile of serum tumor markers for small cell lung carcinoma (SCLC): Very high NSE, Thioredoxin (Trx), chromogranin A (CgA), synaptophysin, peptide releasing gastrin (ProGRP), ferritin.

NSE- Neuron-specific enolase - is the tumor marker representative of long cell carcinoma (SLC). Its values have a strong correlation between the increased percentage of NSE and the stage of the disease [23].

Thioredoxin (Trx) - Has the highest values in small cell lung carcinoma in peripheral blood [19].

Chromogranin A (CHGA) - It is a marker specific to neuroendocrine tumors, which exhibit elevated levels in small cell lung cancer [24].

Synaptophysin (SYP) is a tumor marker specific to neuroendocrine tumors [24].

Peptide that releases gastrin (ProGRP) - It is a neuropeptide that occurs in neuroendocrine cells outside the stomach, being specific to neuroendocrine tumors [25]. Normal values for an adult are <60 ng/L, with a higher concentration in smokers [23]. In patients with small cell lung carcinoma this marker has very high values.

Serum ferritin is an iron storage protein that occurs in serum and some biological fluids of the body [26]. Although

the mechanism of occurrence of very high levels is not known, in small cell lung carcinoma (SCLC) and metastatic cancers we experience very high levels of serum ferritin [27]. The average survival time of patients with low serum ferritin was found to be longer than that of high levels [26].

Profile of typical/atypical carcinoid tumor serum: chromogranin A (CgA), neuron-specific enolase (NSE), Urinary into 5-hydroxyindoleacetic acid (5-HIAA)

Chromogranin A (CHGA) -It is the most sensitive and convenient marker of neuroendocrine tumors, especially for bronchopulmonary carcinoid tumors [28]. It is an amino acid glycoprotein secreted by neuroendocrine cells [29]. The increased level predicts a generally poor prognosis of survival. It is a tumor marker used for monitoring therapeutic efficiency [30].

Neuron-specific enolase (NSE) -is an enzyme expressed by cells of neural origin and weakly different cells, reflecting the presence of high-grade disease and the increases reflect a high aggressiveness of the tumor [28]. It is a marker with elevated values in bronchopulmonary carcinoid but is not specific to this disease [31].

Urinary and plasma 5-hydroxyindoleacetic acid (5-HIAA) - It is a metabolite of serotonin that is excreted in the urine in tumors that secrete serotonin [28]. It was one of the first markers used to diagnose neuroendocrine tumours - pulmonary carcinoid and to monitor treatment response [32]. Plasma 5-HIAA measurement has been shown to correlate well with 5-HIAA urinary, and blood sampling is preferred by patients than in 24-hour urine collections [33,34].

Urinary serotonin and plasma - is a biogenic amine synthesized from the essential amino acid tryptophan [35]. Normally a small amount is found in the plasma [35]. Serotonin is detected in increased amounts in blood and urine tests [33].

Discussion

Clinical Implications of Early Molecular Diagnosis in Lung Cancer leads to a cascade of investigations in order to make a personalized diagnosis. After establishing the personalized diagnosis, a personalized treatment is required. Following the thorough analysis of the literature, we concluded that the following steps are necessary:

- ✓ Molecular diagnosis of bronchopulmonary cancer is based on a molecular profile, by examining several circulating analytes, most serological, but also from other biological fluids. Examination of a single analyte for molecular diagnosis shall not be recommended. The association of the results of the analytes (hormones, biologically active substances and tumor marker) established for each diagnostic profile, gives the necessary information. The role of these analyses is to detect the disease at an early stage, increasing life expectancy by initiating effective personalised treatment, reducing hospital costs and social reintegration of patients.



- ✓ Screening of the population with risk factors, by detection of tumor markers – Increased morbidity and mortality among the population with lung cancer – the 1st place in the world in neoplastic diseases, leads us to find new ways of screening the population. So, such a process is required for smokers and other people with risk factors.
- ✓ Imaging investigations used for the detection of lung tumors; biological sampling of tumor formations – the high level of these tumor markers causes additional imaging investigations by pulmonary X-rays, tomography computer, PET-CT. Tumor formations detected imaging are subsequently biopsied by various invasive methods: bronchoscopy, guided imaging punctures, thorascopies, in order to confirm histopathological diagnosis.
- ✓ Histopathological examination – remains the main analysis for the diagnosis of certainty of bronchopulmonary cancer. Biological samples obtained from tumor tissues by biopsy and/or cytology are necessary to the histopathologist to establish the personalized diagnosis and to direct the therapists – surgeon and oncologist – to apply the effective personalized therapeutic attitude.
- ✓ The role and place of the Thoracic Surgery Surgeon is essential both in diagnosis and in therapeutic attitude. Together with the members of the oncology committee, first-line therapeutic conduct will be established where the role of the thoracic surgeon is essential in determining the surgical opportunity. Our experience is highlighted in the specialized work.
- ✓ Control of the therapeutic efficiency of personalized treatment – can be achieved by analyzing markers from biological fluids, followed by imaging investigations.

Predicting – Increased life expectancy among the population with bronchopulmonary cancer can be achieved through screening, with early detection of bronchopulmonary cancer. This method can initiate effective custom treatment schemes.

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