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REVIEW PAPER

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Carcinoembryonic antigen as a tumor marker in lung cancer – is it clinically useful?

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ABSTRACT

Introduction. Lung cancer is the most common cancer in the Western world. Annually there are approximately 1.8 million new cases worldwide. It is characterized by poor prognosis with a 5-year survival of 10-17% depending on the country. Contributing to this poor prognosis is a mainly late diagnosis, as well as a fairly frequent recurrence despite radical surgery. Over the years, scientists have been searching for a tumor marker that would be useful for patients with lung cancer.

Aim. The aim of this study is to discuss the significance of carcinoembryonic antigen (CEA) in the diagnosis, prognosis of the disease course, and monitoring patients with lung cancer.

Methods. Review of the literature using the PubMed database, Termedia, Via Medica and the key issue: carcinoembryonic antigen as a tumor marker in lung cancer.

Conclusions. Serum CEA level can be a reliable complement to the diagnosis of lung cancer. It can be helpful in preoperative prediction of disease course and qualification for adjuvant treatment of non-small cell lung cancer especially adenocarcinoma. Trends and normalization of CEA during chemotherapy have an impact on progression-free survival and overall survival (OS) of patients. Various available publications describe CEA as a marker for metastatic lung cancer, which is the most specific for metastasis in the liver and brain.

Key words. carcinoembryonic antigen, lung cancer, prognostic factor, tumor marker

Introduction

Lung cancer is the most common malignant tumor in highly developed countries, but it is also becoming a major health problem in developing countries. According to the data published in 2012 by the International Agency for Research on Cancer (IARC), around 1.8 million new cases of lung cancer are diagnosed worldwide, which constitutes 13% of all malignant tumors. This cancer is the leading cause of neoplastic death in men and is the second most common cancer in women[1]. It is estimated that the number of lung cancer cases has increased by 51% worldwide since 1985 (44% in men and 76% in women)[2], and WHO indicates that the number of deaths will continue to increase, which is mainly the consequence of a significant increase in tobacco smoking. In Poland, according to the National Cancer

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Registry (*Krajowy Rejestr Nowotworów* in Polish), about 21,000 new cases are detected annually, which accounts for 14% of all new cancer cases[3]. A distinctive feature of lung cancer is a poor prognosis with a 5-year survival rate of 17% in the US, 12.3% in Europe, and 10% in the UK[4]. In Poland, it is around 11% for men and 16% for women[5].

Lung tumors are characterized by different microscopic structures requiring different clinical courses and treatment methods. Pathomorphological classification distinguishes two most common types of lung cancer: small cell lung cancer (SCLC) (about 15%) and non-small cell lung cancer (NSCLC), which includes: adenocarcinoma (40%), squamous cell carcinoma (30%), and large-cell carcinoma (10%)[6]. With regard to the numerous subtypes of lung cancer, the most important is the differentiation between SCLC and other types of NSCLC. This distinction is important due to clinical differences regarding the course of the disease, the presence of metastasis and the response to treatment. Small cell cancer is a tumor with high growth dynamics, which is characterized by high sensitivity to chemotherapy and radiotherapy, and because of the early metastatic cancer, the prognosis is bad. Although the cancer cells are small, they show the ability to grow and multiply extensively, which leads to early blood-borne dissemination. Non-small cell lung cancer is moderately susceptible to chemotherapy and radiotherapy. Therefore, surgery plays a major role in radical therapy. Individual subtypes of non-small cell carcinomas also differ. Adenocarcinoma develops from glandular cells located in epithelium lining the airways. It is most often located on the periphery of the lung and sometimes (at an early stage) metastases to the lymph nodes or distant metastases may develop. In addition to chemotherapy, molecularly targeted drugs are used. Squamous cell carcinoma usually locates centrally and is characterized by slower growth and subsequent metastases than other types of lung cancer.[6,7]

A poor prognosis in patients with lung cancer is caused mainly by the late occurrence of clinical symptoms. In 80% of cases, it is diagnosed at the stage of regional spread or distant spread, which results in much less effective treatment. Lung cancer at the dissemination stage is characterized by a 5-year survival rate of around 4%.[4] Moreover, according to various authors, 25–55% of patients suffer relapse after radical surgical treatment.[8-10] A relapse usually occurs in the form of metastases. This suggests the presence of micrometastases, not detected at the time of diagnosis and qualified for treatment [11]. This proves that current conventional diagnostic tests such as X-ray, chest CT scan and bronchofiberoscopy are not sufficient to estimate accurately the stage of the disease. Therefore, over the years there have been opportunities to study markers helpful in diagnostics, and particularly in monitoring treatment.

A tumor marker is a macromolecular substance produced in a tumor cell or by normal host cells in response to a developing tumour, and then excreted to the circulation or other body fluids[12]. An ideal marker is one that meets the following criteria: it can be used in population screening, assessment of the disease, monitoring the treatment and post-treatment control.

In the case of lung cancer, a sufficiently sensitive and specific factor has not been found so far that could become an ideal cancer marker. Regarding the markers that could be helpful for patients with lung cancer it is worth mentioning: CEA, CYFRA 21-1, Ca125, NSE, SCC, Pro-GRP, Ca19-9. With reference to these markers, the most promising but also controversial idea is raised by the carcinoembryonic antigen (CEA).

CEA is one of the most frequently used tumor markers in the world. It was first described by Gold and Feedman in 1965. It is a glycoprotein from the family of membrane proteins with a molecular weight of about 180–200 kDa, produced in the fetal period by cells of the digestive tract and pancreas, and after the birth by cells of the intestines, pancreas and liver. In healthy people, CEA concentration is below 5.0 ng/ml, whereas in people who smoke tobacco, it is higher, but usually does not exceed 10 ng/ml. T1/2 CEA is 2-8 days.[13,14] The increase in CEA in the blood or other body fluids is caused by various factors. This may be an increase in the number of cells producing CEA, an increased synthesis in tumor cells, or a reduction in the possibility of excretion from the body. Although the elevated concentration of CEA was first described in the case of colon cancer which is the leading marker in this case, it is also produced and released into the circulation in other various cancers. Generally, it is most likely produced by adenocarcinomas which are developed in the intestine, pancreas, stomach, thyroid, cervix, endometrium, prostate, urine bladder, breast, lung and it can be also produced by ovarian cancer. An elevated level of CEA may occur in such cancers as: neuroblastoma, sarcomas, lymphomas as well as in the case of cirrhosis of the liver, hepatitis, pancreatitis, peptic ulcer disease, chronic lung diseases, inflammatory diseases of the large intestine, nicotinism, and also during pregnancy.[13] However, these disorders are usually temporary and cause only a slight increase in CEA, rarely above 10 ng/ml.

The aim of this study is to discuss the significance of carcinoembryonic antigen in the diagnosis, prognosis and monitoring of patients treated for lung cancer on the basis of available publications.

CEA in small cell lung cancer

There is no relationship between serum CEA concentration and disease progression, progression-free survival (PFS), overall survival (OS), and no evidence has been found that its level is correlated with an objective re-

sponse to chemotherapy.[15,16] Although in the 1980s, the usefulness of this marker in small cell lung cancer was described, current studies have not confirmed the significance of this marker.

CEA in non-small cell lung cancer

Diagnostics

Due to a low level of sensitivity and specificity, the determination of CEA level is not applicable in screening tests. So far, no marker has been found that is appropriately sensitive to lung cancer, which would be useful in diagnosis.

It is very important to differentiate between benign and malignant lung diseases properly. Making an early diagnosis gives a chance for effective treatment of one of the most dangerous cancers in the world, however, based on the available basic tests, targeting the diagnosis to detect cancer early is difficult. Clinical symptoms of lung cancer appear late, which together with diagnostic difficulties result in the fact that only 20% of patients can undergo surgery. Therefore, a lot of research was done in order to search for a marker that would help in distinguishing malignant lung diseases. It was proved that serum CEA concentration is significantly higher in the case of malignant neoplasms of the respiratory system and it was found that their much higher values were observed in adenocarcinomas.[17,18] Therefore, CEA may be a useful indicator in the diagnosis of lung cancer, especially adenocarcinoma. The results of the above studies indicate that the increase in serum CEA concentration may become a reliable complement to computed tomography in the diagnosis of lung cancer, where CEA may appear as a single tumour marker or in a panel with other markers such as CYFRA 21-1, NSE. The combination of several markers increases the clinical effectiveness of diagnostics, but it also increases its costs.[17-19]

It was observed that elevated concentrations of CEA in bronchoalveolar lavage (BAL) fluid may also be useful in the diagnosis of lung cancer. Therefore, Ghosh, Charalabopoulos and Dąbrowska, based on performed analyses, indicate that in regards to non-small cell lung cancer, the CEA concentration in bronchoalveolar lavage fluid is significantly higher than in mild lung diseases.[20-22] However, it should be noted that it is also higher in people who smoke, which means that tobacco causes cell changes in the bronchial cells resulting in an increase in CEA secretion.[20,21,23] Charalabopoulos suggests that cigarette smokers diagnosed with mild lung diseases and high levels of CEA in BAL may be predisposed to develop lung cancer in the future.[21] Based on the above studies, it can be concluded that the measurement of carcinoembryonic antigen in BAL may be useful in the diagnosis of non-small cell lung cancer, but not as a single test, but as a complement to standard tests.

Pre-operative CEA concentration

Numerous reports indicate that elevated pre-operative serum CEA concentration is associated with more advanced cancer disease and the risk of recurrence.[24-26] A study conducted by Tomita et al. indicated that CEA level is an independent prognostic factor in patients with adenocarcinoma of the lung and confirming its growth before the operation suggests a worse prognosis despite an early diagnosis.[24] Matsuoka et al. observed a relationship between elevated levels of CEA for stage I lung adenocarcinoma, and a shorter progression-free survival (PFS), total survival (OS) and an early recurrence. This correlation was not confirmed in the case of squamous cell carcinoma.[25] Buccheri noted that the CEA level> 10 ng/ml at stage Ia to IIb was associated with a 67% risk of early recurrence of lung cancer after a radical surgical treatment.[26] Okada et al. emphasized that not only the elevated concentration of CEA is significant in the prognosis, but also the lack of normalization of the marker after the surgery was characterized by a worse outcome.[27] Muley et al. found evidence, after analyzing the significance of the TMI index (tumour marker index) presenting the geometric mean of normalized values of CEA and CYFRY 21-1, that elevated TMI values are a prognostically negative survival rate in non-small cell lung cancer in stage I.[28] Both Buccheri and Okada together with Muley did not observe differences between histological types, i.e. adenocarcinoma and squamous cell carcinoma. On the other hand, other authors stated that neither the evaluation of CEA level nor the TMI index are statistically significant in a prognosis regarding the course of the disease, and elevated CEA is not associated with a worse prognosis.[29]

In the course of publishing subsequent works, the question has appeared whether there is a relationship between elevated CEA concentration, histological type of lung cancer, and a worse prognosis. Some researchers showed a relationship between elevated levels of CEA and a worse prognosis only for adenocarcinoma of the lung.[25] However, there were also studies showing that in the case of squamous cell carcinomas, the CEA concentration> 5 ng/ml concerned 26% of patients in stage IIIB and 53% in stage IV.[30] Many authors have not found a significant difference between histological types of lung cancer. In some publications, the researchers analyzed patients with non-small cell lung cancer without division into particular histological types. Moreover, the opinion of some researchers that CEA plays a role in predicting metastases to mediastinal lymph nodes[31,32] has also been an issue of concern, while others have denied this statement.[24]

Monitoring the treatment

Several studies have suggested that CEA levels may become a predictor of response to the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib in patients with adenocarcinoma of the lung. Some authors claim that an elevated concentration of CEA before starting therapy may indicate a better response to TKI treatment, longer PFS and OS.[33-36] In their work Romero-Ventosa et al. reported that patients with CEA> 5 ng/ml indicated a significantly better response to treatment with inhibitors, and the median overall survival was 10.2 months.[35] The mechanism of this phenomenon has not been clarified. Jin et al. noted that the frequency of EGFR mutations was significantly higher in a group of patients with elevated levels of CEA, compared to the group with proper levels. In the group of patients with CEA <5 ng/ml, the frequency of EGFR mutations was 55%, whereas in the group with CEA> 20 ng/ml – 82%. On this basis, it can be concluded that elevated serum CEA concentration may help to predict the presence of EGFR mutations.[37] Moreover, it is worth mentioning that there are other studies that contradict the above data, indicating the opposite conclusions. Kappers et al. argue that in patients treated with gefitinib or erlotinib, it is observed that low concentration of CEA indicates a better prognosis.[38] Moreover, Chen et al. claim that patients with CEA levels> 32 ng/ml have a shorter PFS and OS, but not only the antigen output level is important, but also the tendency and normalization during treatment of the first TKI line. Those patients who had a decrease in CEA by more than 35% during the month with normalization had the longest PFS and OS.[39] Other studies also demonstrated the prognostic significance of CEA during standard chemotherapy (the inclusion criterion was the output concentration CEA> 10 ng/ml in patients in III-IV stage) and it was observed that the decrease by 14% correlated well with OS and PFS, while the increase by more than 18% might be a measure of disease progression.[40]

CEA as a metastatic marker

The carcinoembryonic antigen is helpful in detecting recurrences or distant metastases, mainly in colorectal cancer, but it may concern many cancers. The positive predictive value of CEA increase for confirmation of progression is over 90% and it can be considered as a universal marker of tumour metastases.[41] In many metastatic patients, regardless of the location of the primary disease, an increase in the marker is observed, even if it was normal before the treatment. This dependence has led to many studies to explain the phenomenon of carcinoembryonic antigen in metastatic processes. We know that neoplastic transformation induces intense CEA production. Tumour cells released from the primary tumour have significant amounts of the cellular form of CEA on their surface, which undergoes exfoliation and creates a free soluble form of the antigen. It is the content of the free form that increases at the onset of the neoplastic process or after its treatment - as an indicator of recurrence.[41] The relationship between CEA concentration and a poor prognosis forced scientists to conduct studies on the participation of the CEA cellular form in metastasis. It has been proven that as a result of homotypic interactions, it can aggregate tumour cells circulating in the blood, thus it increases their survival and makes them easier to remain in the bloodstream.[41,42] Researchers found receptors presenting the ability of bounding CEA on Kupffer cells in the liver and alveolar macrophages.[43] In conclusion, CEA acts as an adhesion molecule and "chemo-attracting", it can activate Kupffer cells, stimulate IL-1β, IL-6 and TNF-α and thus promotes adhesion of tumour cells to endothelial cells and facilitates the migration process resulting in tumour spread.[44,45]

It should be noted that many researchers confirmed the fact that high concentration of CEA is much more frequently related to patients with the M1 feature compared to M0. On this basis it seems reasonable to claim that CEA is associated with the development of metastases and a worse prognosis in advanced lung cancer.[46-50] There was a clear relationship between the CEA level and liver metastases, then the highest serum CEA concentrations were also observed.[46] Lee et al., based on the analysis of the history of 377 patients newly diagnosed in stage IV of non-small cell lung cancer, reported that elevated levels of CEA were strongly associated with generalized metastases in advanced lung cancer. This correlation was evident in adenocarcinoma type, with bone metastases, CNS, lungs and mediastinal lymph nodes. Very high concentrations of CEA (above 100 ng/ml) indicated a relationship with metastases to the abdomen and pelvis.[46] Arrieta et al. claim that the high concentration of this antigen is an independent prognostic factor for the development of CNS metastases in advanced non-small cell lung cancer. In his study, the specific factors were adenocarcinoma type and CEA concentration > 40 ng/ml. He showed that within 2 years of diagnosing lung cancer in stage IIIB-IV, 67% of patients with CEA> 40 ng/ml and 20% with CEA <40 ng/ml had brain metastases. In addition, he suggested that surface expression of CEA in tumour cells may be a pathophysiological mechanism of invasion of neoplastic cells to the CNS by bounding with immunoglobulins and transport across the blood-brain barrier.[47] It should also be taken into account that CEA is usually measured at higher concentrations in the cerebrospinal fluid of patients with brain metastases.[48] Other authors also emphasize the relationship between this marker and metastases in the CNS.[49] In turn, other researchers who also demonstrate the prognostic signif-

icance of CEA in predicting neoplastic dissemination, did not observe the relationship between it and the site of metastases. They were found in the bones, OUN, liver, adrenal glands. However, it was indicated that the concentration of CEA is significantly higher in the case of adenocarcinoma of the lung.[50]

Summary:

The carcinoembryonic antigen as a cancer marker in lung cancer has been analyzed by many researchers since around 1980. On the basis of numerous publications, the following conclusions can be drawn:

1. CEA can become a reliable complement to imaging tests and bronchofiberoscopy in the diagnosis of lung cancer, especially in doubtful cases when differentiated with benign lung diseases.

2. The initial CEA assessment may be helpful in pre-operative prognosis of the course of the disease. A high serum CEA concentration is associated with more advanced cancer, early recurrence and a worse prognosis after a primary resection. Prognostic factors such as CEA or TMI can help distinguish patients with NSCLC who may benefit from adjuvant therapy.

3. The role of CEA in predicting the course of TKI treatment is controversial, but it has been proven that a higher level of CEA correlates with the presence of EGFR mutations necessary for qualifying for TKI treatment and conditioning the response to treatment. Trends and normalization of CEA level during chemotherapy have an effect on PFS and OS of patients with adenocarcinoma of the lung.

4. Some authors emphasize the clinical significance of elevated CEA concentration only for adenocarcinoma of the lung.

5. CEA can be considered as a universal marker of neoplastic metastases also in the case of lung cancer. It is the most specific for the metastases appearing in the liver and in the CNS.

Despite these reports, CEA has not been included in pre-operative assessment, chemotherapy monitoring and follow-up standards. The guidelines of the American Thoracic Society and the European Respiratory Society in lung cancer do not recommend the routine determination of any markers, as well as the search for distant metastases in imaging studies in asymptomatic patients.51

However, on the basis of the aforementioned publications, it is worth considering performing imaging tests in order to exclude metastases in patients with elevated serum CEA concentration, even in the absence of clinical symptoms. This would allow the researchers to identify a group of patients with an increased risk of disease spreading. Despite so many studies and publications, there is still no results that could unambiguously confirm the usefulness of establishing serum CEA concentration in patients with lung cancer and would convince the American Thoracic Society and the European Respiratory Society to change their position.

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