



Professional article

ACTA FAC MED NAISS 2007; 24 (2): 65-69

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A ROLE OF CYFRA 21-1 AMONG TUMOR MARKERS FOR NON-SMALL-CELL LUNG CANCER

SUMMARY

Lung cancer is the most common cancer worldwide. More than 1,000,000 new cases are registered each year. Therefore, it is not surprising that it has become a global problem, and a major focus of interest of thoracic oncologists on both hemispheres.

The aim of this assay is to review the main characteristics of available tumor markers used in NSCLC.

CYFRA 21-1 shows the best sensitivity in NSCLC and higher sensitivity for squamous cell carcinoma than other histological subtypes, a good correlation with disease extent, and a strong specificity in non-malignant lung diseases. Before any treatment, CYFRA 21-1 shows the highest sensitivity for squamous cell carcinoma when compared to CEA, NSE, CA 19-9, CA 15-3 and CA 125. Therefore, CYFRA 21-1 is the marker of first choice in NSCLC. However, this marker is not suitable for early diagnosis of NSCLC.

Combinations of markers, identified either by standard immunohistochemical techniques or by more novel complementary DNA arrays may prove quite useful for diagnosis and treatment of lung cancer.

Key words: non-small-cell lung cancer, tumours markers, clinical practice

INTRODUCTION

Lung cancer is the most common cancer worldwide. More than 1,000,000 new cases are registered each year (1). Therefore, it is not surprising that it has become a global problem, and a major focus of interest of thoracic oncologists on both hemispheres. Its incidence makes it a major problem of public health. It is the most frequent cause of cancer-related deaths, representing 28.2% of all cancer deaths (2).

Of patients who initially present with lung cancer, 55% have distant metastatic disease, 30% have disease spread to regional lymph nodes, and only 15% have disease confined to the lung (2).

The achievements we made during the last several decades enabled incremental, but continuous, improvements in this field. With the wide introduction of computerized tomography (CT) scanning in the diagnostic approach of these tumors, we become capable of better imaging and, consequently, better clinical staging. Coupled with CT is a recent introduction of positron emission tomography (PET) scanning, combining morphological and functional imaging. These two imaging approaches are increasingly being combined in both diagnostic and therapeutic approaches. They also serve as a tool for evaluating treatment response. While the number of centers using this approach is still limited, it is not hard to imagine it bursting into

the future with consequential changes in image-oriented treatment decisions focusing more on tumor physiology.

The main four histological types of lung cancer are squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma-SCLC. The first three subtypes are generally combined on the heading of non-small-cell carcinoma (NSCLC) and account for approximately 80% of lung cancer (3).

Surgical resection is the accepted treatment for patients with stage I and II NSCLC, with full lobar or greater resections preferable to sublobar resections. The performance of systematic mediastinal lymph node dissection improves the accuracy of staging and may have therapeutic benefits. There is no proven benefit of adjuvant or neoadjuvant chemotherapy for early stage NSCLC. At least 50% of these patients will develop local relapse or distant metastases (4).

Furthermore, 70% of patients are inoperable at the time of presentation because of either locally advanced disease or distant metastases (5). Most patients with advanced disease ask for a specific treatment even if the possible benefit expected by currently available chemotherapy regimens is modest.

Purpose of tumor markers in lung cancer

Large programs of screening in the population have failed to demonstrate any benefit for early detection of lung tumors and the vast majority of patients are diagnosed either by chance or when they present symptoms. Currently, there are no specific tumor markers enabling detection of lung cancer at an early stage.

On the other hand, the diagnosis of relapse after curative treatment or the evaluation of the objective effect of systemic therapies are often difficult to determine and serum tumor markers can help in management of NSCLC as it is the case with other malignancies.

The ideal profile of tumor markers should include sensitivity, specificity, prognostic value and ability to detect response and early recurrences.

The aim of this assay was to review the main characteristics of available tumor markers used in NSCLC.

Characteristics of clinically used tumor markers in lung cancer treatment

Carcinoembryonic antigen (CEA) is the most frequently used tumor marker in adult malignancies. Its sensitivity is about 30% in limited NSCLC and 55% in advanced NSCLC. Levels of

CEA suggest tumor size and their progression is generally related to disease outcome. It should be noted that this marker can be substantially increased in smokers (6).

Neuron specific enolase (NSE) was reported as highly suggestive of neuroendocrine tumors. It is considered as a marker of choice in small lung cancer where its sensitivity ranges 50-80% according to disease extent. Nevertheless, an increase of NSE can be expected in NSCLC. It has been suggested that it may be associated with neuroendocrine component of the tumor. In fact, NSE is frequently elevated in all subtypes of advanced NSCLC (7).

Carbohydrat-antigen 19-9 (CA 19-9) is generally used as tumor marker in digestive, mainly pancreatic malignancies. Nevertheless, it has no clear specificity and does not seem to have any prognostic value.

Carbohydrat-antigen 15-3 (CA 15-3) is a tumor marker mainly used in the therapeutic management of breast cancer. It can also be elevated in other malignancies especially in advanced NSCLC.

Carbohydrat-antigen 125 (CA -125) is a tumor marker mainly used in diagnosis and follow-up of ovarian tumors. It is frequently elevated in case of pleural effusions in case of lung tumors.

CYFRA 21-1: Clinical characteristics of cytokeratins

The cytokeratins are a part of intermediate filament protein group, which is a major component of the cell cytoskeleton. There are 20 different cytokeratins with molecular weights ranging from 40 to 70 Kilodaltons (KD), classified according to their isoelectric point into two types: acid (type I), basic (type II). Low molecular weights are found in simple epithelium and heavy molecular weights are found in epidermis. Under the influence of intrinsic or extrinsic factors, each cell will express different types of cytokeratins in the course of its evolution. These factors have an important role in epidermal differentiation. The type of cytokeratin synthesized by a cell is also affected by the growth and differentiation rate.

CYFRA 21-1 (cytokeratin fragment 21-1) is a fragment of cytokeratin 19 which is a part of cytoskeleton in epithelial cells, and can be found in an overexpressed way in tumors of epithelial origin.

CYFRA 21-1 shows the best sensitivity in NSCLC and higher sensitivity for squamous cell carcinoma than other histological subtypes, a good correlation with disease extent, and a strong specificity in non-malignant lung diseases. Before any treatment, CYFRA 21 – 1 shows the highest sensitivity for squamous cell carcinoma when

compared to CEA, NSE, CA 19-9, CA 15-3 and CA 125. Therefore, CYFRA 21-1 is the marker of first choice in NSCLC (8, 9).

For the diagnosis of adenocarcinoma, the combination of the markers CYFRA21-1 and CEA is recommended (10).

However, this marker is not suitable for early diagnosis of NSCLC (8).

Tumor marker analyses can be of great importance in the follow-up patients under treatment. Post-surgical values show that CYFRA 21-1 is closely correlated with radical surgery of the tumor mass. Nevertheless, a residual tumor mass without marker production cannot be excluded completely. Furthermore, CYFRA 21-1 gives, when initially increased, an accurate estimate of the effectiveness of chemotherapy and radiotherapy of NSCLC, but cannot differentiate between complete and partial remission with ultimate certainty (11-13).

Serial measurement of serum concentration of tumor markers during follow-up can serve for early detection of tumor progression. This fact was proved by NSE in SCLC and by CYFRA 21-1 in squamous cell carcinoma. There are different opinions about the clinical value of such an early recognition of tumor progression.

CONCLUSION

Physicians are still looking for ideal tumor markers in malignant diseases, useful for patient screening, early diagnosis, prognosis and therapeutic monitoring. Most tumor markers tested in NSCLC are today of poor or moderate sensitivity and specificity and cannot be proposed for screening.

During the past ten years, considerable insight has been obtained regarding the molecular basis of lung cancer. As a result, numerous studies have been performed to ascertain if specific mutational events have unique prognostic significance. In particular, these transitional efforts have focused on common aberrations regarding expression of genes regulating cell/cycle progression, apoptosis, invasion and metastasis.

Many growth factor/receptor systems are expressed by either the lung tumor or adjacent normal cells, thus providing autocrine or paracrine growth stimulatory loops. These are excellent new therapeutic targets. Overexpression of epidermal growth factor receptor (EGFR) is observed in approximately 70% of NSCLCs and may be a prognostic factor for poor survival (15). Coexpression of EGFRs and their ligands, especially transforming growth factor – α , by lung cancer cells indicates the presence of an autocrine growth factor loop (16). Gefitinib (ZD 1839, Iressa) is a specific inhibitor of EGFR-tyrosine kinase that demonstrates antitumor activity in patients with NSCLC. Monoclonal antibodies against the extracellular domain of EGFR, such as C225, are another way of therapeutic targeting this key pathway (17).

ERBB2 (HER 2/neu) is highly expressed in more than a third of NSCLCs, especially adenocarcinomas, although gene amplification as seen in breast cancer is not usually the underlying mechanism in lung cancer. A meta-analysis suggested that overexpression of ERBB2 is a factor of poor prognosis for survival in NSCLC (18). Trastuzumab (Herceptin®), a recombinant humanized monoclonal antibody that recognizes HER2, thus blocking its activity, is being tested for efficacy in NSCLC as a single agent or in combination with chemotherapy (19).

Overexpression of epidermal growth factor receptor (EGFR), particularly ERBB2, correlates with survival in lung cancer patients after resections. Increased expression of mitogen-activated protein kinase as well as K-RAS and p53 mutations correlate with adverse outcome in lung cancer patients (14-15, 20-22).

Given the molecular heterogeneity of lung cancer, it is not surprising that no single biomarker has emerged that uniformly correlates with prognosis in lung cancer patients. On the other hand, combinations of markers, identified either by standard immunohistochemical techniques or by more novel complementary DNA arrays may prove quite useful for diagnosis and treatment of lung cancer.

Nevertheless, together with this prognostic factors, a tumor marker can be used to monitor the clinical course, treatment and follow-up of patients.

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ULOGA CYFRA 21-1 MEĐU TUMORSKIM MARKERIMA ZA ODREĐIVANJE NEMIKROCELULARNOG KARCINOMA PLUĆA

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SAŽETAK

Karcinom pluća je širom sveta najčešći malignitet. Preko 1000000 novih slučajeva otkrije se tokom svake godine. Zbog toga ne čudi što je opšti problem i glavno interesovanje grudnih onkologa na obe hemisfere.

Cilj ovog rada bio je da prikaže glavne karakteristike dostupnih tumorskih markera koji se mogu koristiti u kliničkoj praksi NSCLC.

CYFRA 21-1 je senzitivn u NSCLC, posebno u slučaju skvamocelularnog podtipa, ukazujući na proširenost bolesti i visoko je specifičan među bolestima pluća nemaligne etiologije. Pre započetog bilo kog lečenja, CYFRA 21-1 pokazuje visoku specifičnost među skvamocelularnim karcinomima u odnosu na CEA, NSE, CA 19-9, CA 15-3 i CA 125. Zbog toga je CYFRA 21-1 tumorski marker izbora u slučaju NSCLC. Za adenokarcinome preporučuje se kombinacija markera CYFRA 21-1 i CEA. Međutim, ovaj marker nije pogodan za ranu dijagnozu NSCLC.

Jedino kombinacija markera, identifikovanih bilo imunohistohemijski ili komplementarnim novim DNA istraživanjima, mogu biti vrlo korisni za dijagnozu i lečenje karcinoma pluća. Bez obzira na sve, sa navedenim prognostičkim faktorima, tumorski marker se može koristiti za nadgledanje kliničkog toka, lečenja i preživljavanje bolesnika.

Ključne reči: nemikrocelularni karcinom pluća, tumorski markeri, klinička praksa