Circulating Biomarkers for Lung Cancer

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Abstract

Ideal characteristics of tumor markers and their role in clinical practice are discussed. Measuring markers in screening programs resulted inefficient, while the pathological elevation of one or more markers may be virtually diagnostic of lung cancer in appropriate clinical setting. The elevation of CEA, NSE, TPA and other presented, appears particularly useful in the evaluation of the extent of disease, and may correlate with prognosis, as well as in postsurgical follow-up and monitoring therapy.
Key words: Tumor markers, CEA, NSE, TPA, lung cancer, follow-up.

Riassunto

Vengono discusse le caratteristiche ideali dei marcatori tumorali ed il loro ruolo nella pratica clinica. Il dosaggio dei marcatori è apparso privo di efficacia nei programmi di screening sulle popolazioni a rischio. L'aumento patologico di uno o più marcatori può, d'altra parte, risultare diagnostico per carcinoma del polmone solo in rare specifiche situazioni cliniche, ma il rialzo del CEA, NSE, TPA ed altri presentati, appare particolarmente significativo nella valutazione della estensione di malattia, ed è pertanto correlabile alla prognosi, così come nel follow-up postchirurgico e nel monitoraggio della terapia oncologica.
Parole chiave: Marcatori tumorali CEA, NSE, TPA, carcinoma del polmone, follow-up.

Neoplastic cells produce and release several substances. Some molecules are tumor-specific and can be produced by few or several types of cancer. Other substances are produced by tumor cells in larger amounts than normal cells. Occasionally, normal cells release abnormal quantities of their products in response to the invasion of cancer cells. Independent of the mechanism of production, an array of biological substances "marks" the existence, response, or progression of certain types of cancer. Such substances are called "tumor markers".

Although the term tumor marker is sometimes more broadly defined to include any tumor cell-surface antigen, intracellular protein, and even chromosomal and genetic abnormalities detectable in a tumor pathologic specimen, in this article the word "tumor marker" refers to substances that are present in the blood of patients with cancer and suitable for an easy and inexpensive serum test. Several characteristics define an ideal tumor marker.

- The ideal marker should be produced preferentially by tumor cells and readily detectable in body fluids.
- It should not be present in health or in benign diseases.
- It should be present frequently enough and early enough in the development of a malignancy to be useful in screening for that cancer.
- Its quantity in the blood should directly reflect the bulk of the tumor and yet be detectable when the tumor is in a subclinical phase.
- Finally, the level of the ideal marker should correlate with the results of anti-cancer therapy and the ultimate prognosis.

Tumor markers are not only of significance to the researcher in developing theories concerning the biology of the malignant process, but also to the clinician in the management of patients with cancer. For example, they may be useful in the diagnosis and histopathologic classifications, as well as in staging, prognostication, and therapy monitoring (including the evaluation of tumor response and early relapse). Well-known examples of clinically useful markers are amines in carcinoids and pheochromocytomas, and the M-component in myeloma. In recent years, human chorionic gonadotrophin and α-fetoprotein have contributed significantly to the diagnosis and treatment of germ cell tumors, including testicular cancer.

The expression of lung tumor markers has been known for many years[1-3]. However, new information has been produced during the last decade that has radically changed our knowledge and practice[4-7]. Lung tumor markers fall into several categories including oncofetal proteins,

structural proteins, enzymes, membrane antigens, peptide and non-peptide hormones, and other tumor-associated antigens. Table I outlines a possible classification and a list of the most popular markers for lung cancer during the last 10 years.

Essentially, lung tumor markers play four potential roles in clinical practice:

1) screening
2) diagnosis
3) assessing the stage of disease and prognosis
4) monitoring anti-cancer therapy.

Screening

Screening involves the search for disease in asymptomatic individuals. The low frequency of patients with cancer in any asymptomatic population requires high validity of the measurement method. The value of a screening test for cancer involves an evaluation of its sensitivity. Because the prevalence of any one cancer in any one individual at a specific time is low, a marker that is found in a small percentage of patients with cancer is unlikely to be useful. The ideal marker is elevated in virtually all cases and in

Tab. I. – A WORKING CLASSIFICATION OF LUNG TUMOR MARKERS WITH REFERENCES (LITERATURE OF THE LAST 10 YEARS).

Classification	*Tumor marker*	*Relevant studies*
Oncofetal proteins	Carcino-embryonic Antigen (CEA)	Bergman et al., 1993[8] Body et al., 1990[9] Buccheri et al., 1986-93[10-12] Diez et al., 1996[13]) Ferrigno et al., 1992[14] Icard et al., 1994[15] Jaques et al., 1988[16] Jarvisalo et al., 1993[17] Johnson et al., 1993[18] Jorgensen et al., 1989[19] Laberge et al., 1987[20] Niklinsky et al., 1992[21] Picardo et al., 1994[22] Plebani et al., 1995[23] Stieber et al., 1993[24] Walop et al., 1990[25]
(Structural proteins (Cytokeratins)	Tissue Polypeptide Antigen (TPA)	Buccheri et al., 1986-95[10-12, 26-29] Correale et al., 1994[30] Ferrigno et al., 1992[14] Gronowitz et al., 1990[31] Mizushima et al., 1990[32] Plebani et al., 1995[23] Stieber, et al., 1994[33] van der Gast et al., 1991-5[34, 35]
	Cytoketarin 19 fragment (Cyfra 21-1)	Bombardieri et al., 1994[36] Lai et al., 1996[37] Muraki et al., 1996(38) Niklinski et al., 1995-6[39, 40] Plebani et al., 1995[23] Pujol et al., 1993-1996[41, 42] Rastel et al., 1994[43] Stieber et al., 1993-4[24, 33] Sugama et al., 1994[44] van der Gast et al., 1994-5[35, 45] Wieskopf et al., 1995[46]
	Tissue Polypeptide-specific Antigen (TPS)	Marino et al., 1992[47] Pujol et al., 1996[42] Stieber et al., 1994[33]
Enzymes	Neuron-specific Enolase (NSE)	Ariyoshi et al., 1986[48] Bergman et al., 1993[8] Ferrigno et al., 1990[49] Hardling et al., 1990[50] Jaques et al., 1988[16] Jarvisalo et al., 1993[17]

Classification	*Tumor marker*	*Relevant studies*
		Johnson et al., 1993[18] Jorgensen et al., 1988-96[19, 51-54] Milleron et al., 1990[55] Plebani et al., 1995[23] Quoix et al., 1993[56] Splinter et al., 1987[57] Stieber et al., 1993[24] Szturmowicz et al., 1993[58] van der Gaast et al., 1991[34] van Zandwijk et al., 1992[59]
	Lactate dehydrogenase (LDH)	Buccheri et al., 1986[10] Khono et al., 1992[60] Johnson et al., 1993[18] Jorgensen et al., 1989[19] Sagman et al., 1991[61] van Zandwijk et al., 1992[59]
	Creatin-phosphokinase isoenzyme BB (CPK-BB)	Ariyoshi et al., 1986[48] Jaques et al., 1988-93[16, 62]
Membrane antigens	Neural cell adhesion Molecule (NCAM)	Jaques et al., 1993[62]
	soluble Interleukin-2 receptors (sIL2-R)	Buccheri et al., 1991[63] Chan et al., 1993[64] Ginns et al., 1990[65] Yamaguchi et al., 1990[66] Poulakis et al., 1991[67] Tisi et al., 1992[68]
Hormones	β-HCG	Buccheri et al., 1986[10] Walop et al., 1990[25]
	Gastrin releasing peptide (GRP)	Takada et al., 1996[69]
Other tumor-associated antigens	Squamous cell Carcinoma Antigen (SCC-Ag)	Body et al., 1990[9] De Cos et al., 1994[70] Diez et al., 1996[13] Ebert et al., 1992-6[71, 72] Mino et al., 1988[73] Niklinsky et al., 1992[21] Plebani et al., 1995[23] Sanchez et al., 1994[70] Stieber et al., 1993[24]
	CA 125	Diez et al., 1991-96[13, 74, 75] Kimura et al., 1993[76] Molina et al., 1994[77]
	CA 19-9	Buccheri et al., 1987[11] Niklinsky et al., 1992[21] Stieber et al., 1993[24]
	CA 242	Pujol et al., 1993[78]
	CA 15-3	Stieber et al., 1993[24]
	Chromogranin A	Berg et al., 1989[79] Johnson et al., 1993[18] O'Connor et al., 1986[80] Sobol et al., 1986[81]
	Ferritin	Cox et al., 1986[82] Ferrigno et al., 1992[14] Muller et al., 1985[83]

the early stages of malignancy. Most current markers are rarely elevated in early stages and cannot be used in this way. The specificity of a marker is also important. False-positive results appear unacceptable from the ethical and economical point of view because the clinical confirmation of positive results is usually invasive. Unfortunately, no tumor marker is sensitive enough nor reliably specific to be used as a screen. A follow-up study of lung cancer occurrence was done in individuals who had health examinations during a large-scale Finnish health survey[17]. Four lung tumor markers were measured in serum specimens collected. Assuming a cancer prevalence of 1%, the best results would include 50 false-positive results, 8 false-negative results, and only 2 true-positive results[17]. Since the real prevalence of lung cancer in a population of healthy smokers is definitely lower, these figures show the inefficiency and impracticability of measuring markers in screening.

Diagnosis

The identification of a tumor marker that is highly sensitive and specific and that can be used reliably to support the diagnosis of lung cancer remains an important goal of clinical research on tumor markers. The definite diagnosis of bronchogenic carcinoma is cytological or histopathological. However, one could question: is the elevation of any one marker so specific for lung cancer that its presence is highly suggestive for the diagnosis? Is any combination of markers diagnostic? In only a very few narrowly defined clinical settings is the answer yes. Clearly, the presence of suspect clinical signs, appropriate radiological evidence, and highly elevated levels of certain tumor markers in the blood is strongly suggestive for malignancy and recommends further clinical testing. Gail et al.[84, 85] used eight tumor markers in an attempt to distinguish subjects with chronic pulmonary obstructive disease from those affected by lung cancer. Taking into account a disease prevalence of 30%, the best combination of markers (CEA, ferritin and sialic acid) yielded an acceptable positive predictive value (60%), a sensitivity of 36%, and an almost absolute specificity. These data confirm that the pathological elevation of one or more markers, in an appropriate clinical setting, may be virtually diagnostic of lung cancer.

Staging and Prognosis

The third recurrent question, and perhaps the most important, is whether the level of the marker correlates with the stage and prognosis. Lung tumor markers will most likely be elevated in patients with advanced stages of disease. In some cases, the correlation is too close to allow excluding the surgical cure if the plasmatic level of the marker exceeds a given threshold[28]. Therefore, while lung tumor markers are poor tools for screening of asymptomatic patients and may be moderately useful in the differentiation between cancer and nonmalignant lung disorders, their elevation is particularly useful in the evaluation of the extent of disease, leading to a more intense search for metastatic disease. In this sense, those markers whose level of elevation directly reflects tumor mass are mostly useful. At least three classes of tumor markers (CEA, the cytokeratin-derived markers TPA and Cyfra 21-1 in non-small cell lung cancer [NSCLC], and NSE in small cell lung cancer [SCLC]) respond to the above mentioned prerequisite[5-7].
Marker elevations may correlate with the prognosis, but this is usually inseparable from tumor mass. However, there are examples in which the correlation with the prognosis reflects directly the malignant potential of the marker-producing population of cells[86].

Monitoring therapy

The fourth issue concerning the clinical use of lung tumor markers is post-surgical surveillance or the follow-up of patients undergoing medical treatments. Marker elevations may correlate with patients' post-treatment status, as a reflection of their correlation with tumor mass. Because all the markers reported have both false negative and positive results, they cannot be completely relied on when used to monitor the course of disease. Difficulties are due to the heterogeneity of marker expression among different tumors and, additionally, among cancer cells within the same tumor. All studies of markers include subsets of patients whose tumors do not or will never produce the marker. At the time of cancer recurrence, that population is included and may contribute to the false negative rate. In addition, variations in marker expression between primary and metastatic lesions may develop because of the multiclonal process of cancer progression. Finally, the efficacy of therapy is as important in determining the value of a tumor marker as its sensitivity and specificity. If therapy is entirely inadequate, then it is irrelevant that a tumor marker may help to discover clinically silent postoperative recurrences or to recognize rare and shortly lasting responses to chemotherapy. This occurs often (but not always) in lung cancer[87-90].
In monitoring therapy, however, CEA, cytokeratin degradation products, and NSE are the most useful markers[5-7].

Conclusion

Although computerized tomography (CT) scans provide excellent staging and followup data, they are expensive and time consuming. Tumor markers that could be measured by blood tests would be highly desirable. In 1985 no such test was generally available, although

neuron-specific enolase in small cell lung cancer and carcinoembryonic antigen for all types of lung cancer were regarded as potential candidates[1]. Today, both CEA and NSE, along with the new class of cytokeratin derived markers, are convincible tools for staging and monitoring lung cancer. For one of these markers (i.e., TPA), the equivalence with CT has been proven[28, 29]. In future, the combined use of the singly most useful markers (e.g., CEA and TPA in NSCLC and TPA and NSE in SCLC) should be optimized. Guidelines should also be elaborated for the clinical interpretation of results. It is time for a mandatory use of one or more of such markers in national and international therapy protocols.

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