Tumor markers

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Abstract

Searching for early signs of cancer enabling a quick therapeutic and diagnostic intervention is the main concern of all clinicians. As such, tumor markers can be a precious help.

In a short revision concerning this theme, the authors present a practical definition and classification of tumor markers, giving more importance to serological markers as these are more easily obtained. Despite their limitations, the use of these markers in clinical practice is referred to in this work.

Key words: cancer, tumor markers, oncology diagnosis.

Introduction

The determination of tumor markers is undoubtedly one of the major advances in Oncology in recent years, but the search for easily identifiable marks of cancer is not new.

In 1846, an English doctor observed a precipitate in the urine which he linked to the disease known today as multiple myeloma; his finding brought him notoriety, and the proteinuria was named after him. Although a full century passed before it was found that this disease is composed of immunoglobulin light chains, Bence Jones proteinuria is still associated with the disease.

In our century, more precisely from 1928, from the time of Brown and his concept of ectopic hormone produced by tumors, until today, research has focused on the search for "substances" produced or induced by the neoplastic cells that are capable of reflecting tumor activity and growth, allowing or enabling the identification of the presence and evolution of a malignant tumor and even its response to therapy.

Table I lists some of the key events in the history of tumor markers.

Today, when tumor markers are mentioned, one thinks of hormones, enzymes, immunoglobulins, oncofetal proteins and tumor-associated antigens, substances referred to in this paper.

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Definition and classification of tumor markers

The term "tumor marker" applies to any substance of a biochemical nature, produced or induced by neoplastic cells, that can indicate tumor growth and activity, enabling the presence, progression or therapeutic response of a malignant tumor to be identified.[1] Thus, any biochemical parameter that reflects metabolic aspects related to the activity and capacity of a tumor to duplicate can be considered as a tumor marker.[2]

This definition leads to different types of existing markers, so it may be said that tumor markers are molecules produced by neoplastic cells, and can be found either in the tumor itself (surface antigens) or in the blood, urine or other bodily fluids.[3]

To define the usefulness of each of these substances we must think in terms of an ideal marker: what would be expected from an ideal marker?[3,4] It must be sensitive to the point of being elevated in almost all patients; it must be specific to the point of being constantly normal in people who do not have cancer; and its plasma levels must be proportional to the tumor mass, thereby allowing, in addition to easy access, an active evaluation of the progression of the tumor.

This definition implies that a surface tumor antigen or a cell surface tumor marker that is only present in the tissue cannot be a good marker for use in early diagnosis. However, these markers are the ones which, thanks to radio-immunology techniques, can detect the unknown origin of a tumor when metastasis is occurring and the primary tumor remains occult.[5]

Tumor markers can be classified in two major groups.[6] (*Table II and III*): tumor markers on the cell surface and tumor cell markers in the serum.

Two main groups of markers are reported, with

TABLE I

Some historical dates in the search for tumor markers

Year	Author(s)	Contribution
1845	Bence-Jones	Bence-Jones protein
1928	Brown	Ectopic hormone syndrome
1930	Zondek	Human chorionic gonadotrophin (HCG)
1932	Cushing	Adrenocorticotropin (ACTH)
1933	Gutmann & Gutmann	Prostatic acid phosphatase
1949	Oh-Uti	Deletion of blood group antigens
1959	Markert	Isoenzymes
1959	Berson & Yalow	Radioimmunoassay
1960	Newell	Philadelphia chromosome
1963	Abelev	Alpha-fetoprotein (AFP)
1965	Gold & Freeman	Carcinoembryonic antigen (CEA)
1969	Hubner & Todaro	Oncogenes
1975	Kohler & Milstein	Monoclonal antibodies
1980	Multiple Workers	Oncogene probes and transfection
1981	Yunis	Fragile sites
1981	Bast	CA125 in ovarian cancer

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each marker being linked, at the same time, to the type of tumor that is, in most cases, responsible for the existence or aggravation of the tumor, in the cell or serum, respectively.

There are many other classifications, but they all seem to have a more educational or academic, rather than practical interest; from a practical point of view, and bearing in mind the definition of an ideal marker, it seems more important to classify markers by dividing them into three groups.[1,4]

1 – Tumor markers with high specificity and sensitivity

This group includes markers that, although they can be detected in the serum in normal physiological conditions, show clear differences in serum levels in the presence of a particular malignant tumor and in almost all patients who have the tumor. Examples of this marker include:[7]

- β HCG (β human chorionic gonadotropin);
- Calcitonin (present in healthy individuals, but at much higher levels in those with medullary thyroid carcinoma).

2 - Intermediate specificity tumor marker

This marker, which has lower sensitivity, can be detected in all patients with a particular type of tumor and is present in some benign pathologic conditions; the difference between benign and neoplastic pathology is usually identified quantitatively, and based on the way the disease evolves, with assessments at different time points of the disease. This group includes most of the known markers, such as:

- CEA (carcinoembryonic antigen);[7]
- CA 125 (carbohydrate antigen 125);[8]
- Prostatic acid phosphatase;[9]
- Postate-specific antigen (PSA).[9]

3 - Low specificity tumor marker

This group includes substances that are not usually specific, since most of them are also found in non-neoplastic diseases, and sometimes in very high serum concentrations. However, there is interest in monitoring the evolution of known tumors, sometimes enabling the identification of the appearance metastases in a particular tissue. Examples[6] include:

- Alkaline phosphatase (phosphohexose--isomerase)
- Gamma-glutamyl transferase (gamma GT)
- Lactate dehydrogenase (LDH)

Interest of tumor markers for the clinical practice

Despite successive investigations on tumor markers, no ideal marker has yet been defined whose presence, once detected, will help determine the existence of a neoplasm.

In clinical practice, despite the greater ease of access and following the third condition of the ideal marker, the tumor markers most frequently used are those detectable in serum and produced by the tumor, be they embryonic proteins (oncofetal antigens and placental proteins) or a result of differentiated cells (hormones, enzymes, monoclonal immunoglobulins, and segregated tumor antigens).

Unfortunately, most of these markers are not specific to a cancer or a particular type of neoplasm. However, their determination in the serum may be

TABLE II

Tumor markers on the cell surface

Type of tumor	Characteristic antigens on the cell surface
Lymphomas	
B cells	
low malignancy	Ig idiotypic CD5; CD20-22, pan-leukocyte (CD45, T200, LCA)
intermediate/high malignancy	Ig idiotypic CD20-22, pan-leukocyte (CD45, T200, LCA)
T Cell	
mycosis fungoides/ Sezary syndrome	TCR+, CD3+, CD4+, CD25-, CD7-
peripheral T cell lymphoma	TCR+, CD4+, CD8-, CD3+, CD7
adult T cell lymphoma/leukemia	TCR+, CD25+, CD4+, CD8-, HTLV-1+
lymphoblastic lymphoma	TCR+, Tdt, CD2, CD7
Hodgkin's disease	Ki-1 (CD30), Leu M1 (CD15)
Leukemias	
acute lymphoblastic leukemia (ALL)	
common (80%)	Redistribution of the Ig gene, Calla (CD10)
T cell (15%)	CD7, CD2, TCR, Tdt
B cell (5%)	Surface Ig, CD20-22
Acute nonlymphocytic leukemia (ANLL)	Myeloid (My) and monocytic (Mo) antigens
Chronic lymphocytic leukemia (CLL)	
B cell (98%)	Surface Ig, CD20-22, CD5
T cell (2%)	CD2, 2,5 (CD4+8- or Cd4-8+), TCR
Chronic myelogenous leukemia (CML)	LAP, B12, BCR/ABL
Myeloma	Cytoplasmic Ig, beta 2-microglobulin, PCA-1
Carcinoma	
Lung cancers	
non small cell	ACE, CA125, CA19-9, blood group, HMFG
small cell	NCAM, CKBB, EEN, GRP, chromogranin
Breast cancer	ER, PR, EGF receptors, cathepsin, Her-2/neu oncogene
Gastrointestinal cancers	ACE, HMFG, other mucins, blood group antigens
Testicular cancer	β-hCG, AFP
Malignant melanoma	GD2, GD3, S100
Hepatoma	AFP
Sarcomas	Desmin, vimentin
Astrocytomas	Glial fibrillary acidic proteins
Thyroid cancer	
follicular/papillary	Thyroglobulin T3, T4
medullary	Calcitonin, chromogranin, histaminase
Prostate cancer	PSA, PAP, EEn, HMFG
Ovarian cancer	CA125, CA19-9
Phaeochromocytoma	Calcitonin, chromogranin

Abbreviations: Ig = immunoglobulin; TcR = re-distribution of the T-cell receptor gene; FAL = leukocyte phosphatase; β-hCG = beta subunit of human chorionic gonadotropin; AFP = a-fetoprotein; CEA = carcinoembryonic antigen; HMFG = human milk fat globulin; ER = estrogen receptor; PR = progesterone receptor; EGF = epidermal growth factor receptor; NCAM = neural cell adhesion molecule; CKBB = creatine kinase BB isoenzyme; NSE = neuron-specific enolase; GRP = gastrin-releasing peptide (bombesin); PSA = prostate-specific antigen; PAP = prostatic acid phosphatase.
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TABLE III

Tumor cell markers in the serum

Marker	Types of tumor
Hormones	Testicular cancers, choriocarcinoma
Gonadotropin beta subunit	Hydatidiform mole
chorionic	Small cell lung cancer; APUD tumors
AVP, ACTH	Medullary thyroid carcinoma, small cell lung cancer and APUD tumors
Calcitonin	Small cell lung cancer
Gastrin-releasing peptide (bombesin)	
Placental lactogen	Trophoblastic tumors, several carcinomas
Oncofetal proteins	
alpha-fetoprotein	Hepatoma, testicular cancer
Carcinoembryonic antigen (CEA)	Gastrointestinal, breast, lung and ovarian cancer
Enzymes	
L-dopa decarboxylase	Small cell lung cancer
Creatine phosphokinase (BB)	Prostate cancer, small cell lung cancer
Neuron-specific enolase	Prostate cancer, small cell lung cancer, others
Acid phosphatase (prostate-specific)	Prostate cancer
Placental alkaline phosphatase	Uterine, ovarian, breast, and lung cancer
Lysozyme	Non-acute lymphatic leukemia (myelomonocytic and monocytic types)
Serum galactosyltransferase	Gastrointestinal carcinomas, breast and prostate cancers
Lactate dehydrogenase (LDH)	Lymphomas, Ewing's sarcoma, various carcinomas
Segregated tumor antigens	
CA 125	Ovarian cancer, other epithelial cancers
CA 19-9	Various carcinomas
Prostate-specific antigen	Prostate cancer
Other glycosphingolipids	Various carcinomas
β2-microglobulin	Multiple myeloma
Various	
Vitamin B2-binding proteins	Acute myelogenous leukemia or chronic myeloproliferative disease
Immunoglobulin	B-cell lymphoproliferative diseases
Polyamines	Various carcinomas
Chromogranin A	Small cell lung cancer, phaeochromocytoma

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potentially useful for:[2,7]

1 - Screening and early diagnosis in high risk groups
2 - Diagnosis of primary tumor
3 - Evaluation of tumor volume and prognosis
4 - Evaluation of response to therapy
5 - Evaluation or early detection of relapses.

Without intending to perform an exhaustive analysis, we will briefly address each of these items below:

1 - Screening and early diagnosis in high risk groups

Some common malignant tumors occur in a particular type of subject, who can be considered high risk because of the type of neoplasm they have. An example is medullary thyroid carcinoma, which is common among relatives of patients with this type of tumor. This data, and knowledge of a high specificity

marker like calcitonin, create the ideal conditions for early diagnosis.[3]

Also β HCG, whose presence in the serum of men and non-pregnant women is indicative of cancer, enables early diagnosis of patients with testicular germ-cell and trophoblastic tumors, respectively.[7]

Patients with cirrhosis are a high risk group for early liver cancer, in which case alpha-fetoprotein is of great help in early diagnosis, because being an oncofetal protein, its serum levels are negative after birth in normal conditions. If serial determinations of alpha-fetoprotein are found in an individual with cirrhosis and successive increases exceeding 50 mg/dL are detected, early liver cancer should be suspected.[1]

CEA is another oncofetal protein that can also be useful in early diagnosis if, in addition to its high levels, the clinical condition presented and reported by the patient is considered.[6]

Screening for ovarian cancer, a tumor that is usually asymptomatic until it becomes widespread, may be advantageous, especially if the CA 125 determination is used with pelvic echogram.[8]

Knowing prostatic acid phosphatase, which is specific to prostate neoplasm, makes this enzyme a good diagnostic means for the detection of an occult prostate tumor and is very useful, bearing in mind that the incidence of prostate cancer has been increasing. However, given that high rates are found only in advanced stages, early diagnosis is only valid when there is cause for suspicion in the rectal examination.[9]

2 - Diagnosis of primary tumor

Only the markers described as very specific can be applied for this purpose; although all other markers may be useful for diagnosis, in a patient with suspected signs of tumor, an increase of a tumor marker supports the possibility of the existence of a tumor.[10]

In fact, in most cases, circulating tumor markers are used for diagnosis in conjunction with clinical conditions, imaging signs, biopsy of the tissue and even other laboratory results.[4] Some examples are:

A patient with rectal bleeding, anemia, fecal occult blood and elevated serum CEA is very likely to have colorectal cancer;[4]

A youngster with testicular swelling and high levels of a-fetoprotein and β-HCG is likely to have a malignant non-seminal testicular tumor;[7]

Detection of prostate cancer: rectal examination, transrectal ultrasound and the finding of high serum prostate-specific antigen (PSA) have important diagnostic value;[9]

TABLE IV

Use of tumor markers in some neoplasms

Organ	Tumor markers		
Stomach	CA 19-9	CEA	TPA
	5HT	5HIA	5HPT
Liver	AFP	CEA	CA 19-9
	FA	LDH	GAMMA-GT
Pancreas	CA 19-9	CA 50	ELASTASE
	GASTRIN	INSULIN	VIP
Colon and Rectum	CEA	CA 19-9	
Thyroid	CALCITONIN		(+ pentagastrin)
	CEA		Thyroglobulin
Ovary	CA 125 (adenocarcinoma)		
	CEA (T. mucinosis)		
	AFP HGC (teratomas)		
Breast	CA 15-3	CEA	
	Estrogen/Progesteron receptors		

High levels of a-fetoprotein are found in 70% to 95% of hepatomas;[6]

It is suggested that a patient with lung tumor and the presence of high serum levels of neuron-specific enolase has small cell undifferentiated carcinoma; cases of high levels of CA 125 are indicative of large cell undifferentiated carcinoma.[2]

Table IV shows some of the most widely used tumor markers in clinical practice for the diagnosis of some of the most common neoplasms, always within a context of clinical signs and symptoms.

The determination of the markers may also be of help in the diagnosis of some unknown neoplasms. We sometimes find patients with suspected malignant tumor, because they either have paraneoplastic syndrome, or the appearance of metastases without the primitive tumor being detected. In these patients, often with advanced tumor, the determination of markers can be helpful in guiding the diagnosis. Thus, for example, in a patient with condensing bone metastases, the occurrence of elevated PSA levels and/or specific acid phosphatase suggests the existence of prostate cancer.[9]

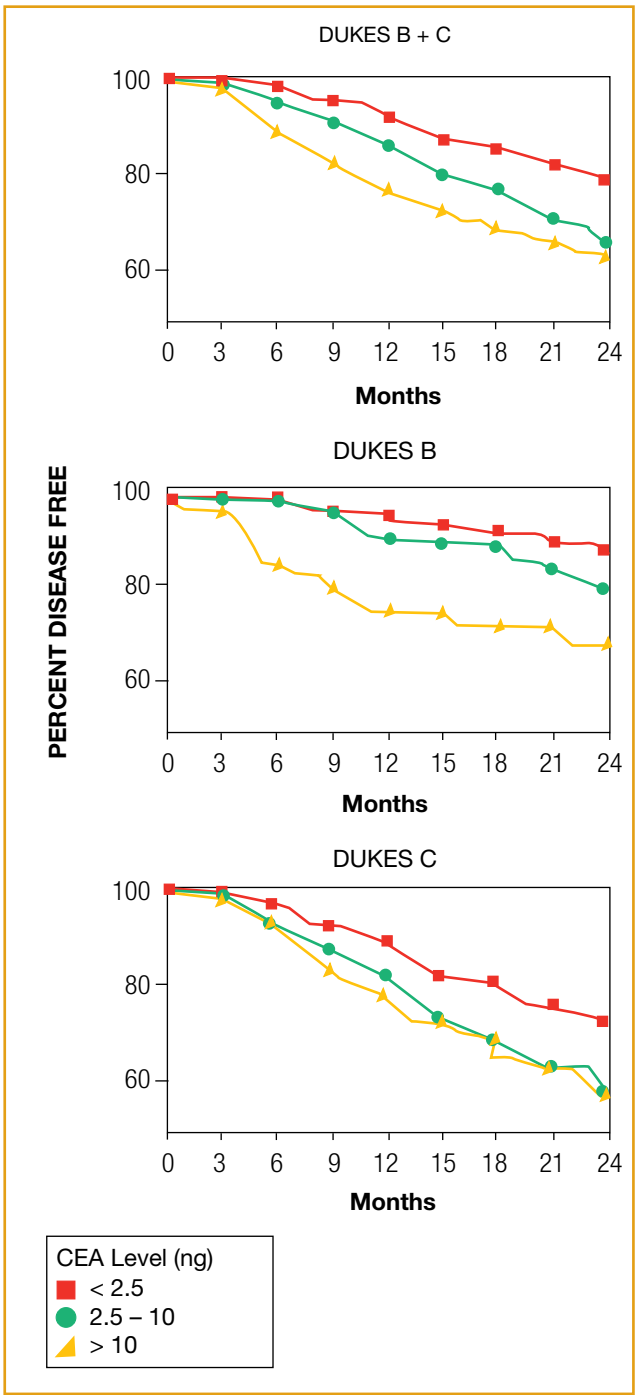

FIG. 1

3 - Evaluation of tumor volume and prognosis

The characteristics of a tumor, cells or others associated with the survival, which are known by the natural history of tumors, constitute parameters that will enable practitioners to determine the risk to the patients; these characteristics are called prognostic factors. They are of interest not only because they indicate the patient's chances of survival, but also because they help practitioners decide on and administer complementary treatments to the surgery, aimed at destroying distant micrometastases.

Of these, the most commonly used are:

- TNM classification;
- Degree of differentiation of the neoplasm;
- Histological type;
- Degree of lymphocytic infiltration.

When observed in association with tumor markers in the serum, the number of tumor cells and vascularization are important, and it is logical to suppose a greater tumor marker synthesis in higher tumor mass (greater number of cells). Moreover, a greater area covered by the increased vascularization would allow for greater release into the circulation, enabling higher levels of serum tumor markers.

It is not uncommon, therefore, to find higher concentrations and percentages of tumor marker positivity in more advanced stages.

For example:

CEA in colorectal carcinoma, according to the Dukes classification, is increased[1] (over 10 ng/l) in Dukes A, 0%; Dukes B, 20-25%; Dukes C, 30-35% (or 60% according to other studies); Dukes D, 80-90% and the prognosis is related not only to the Dukes stage, but to the marker positivity rate, as shown in *Fig. 1*, where Dukes B and C[2] are compared.

In breast cancer, the CEA and its elevated serum levels are associated with the existence of lymphatic invasion. *Table V* shows the prevalence of CEA levels above 10 ng/L calculated for each stage in patients with breast cancer.[3] The majority of markers behave

TABLE V

Prevalence of high levels of CEA in each stage, in patients with breast carcinoma(10)

Stage (TNM)	Patients with high CEA %	Series ranges in %
I	9	0 – 15
II	23	0 – 43
III	46	31 – 64
IV	58	29 – 100

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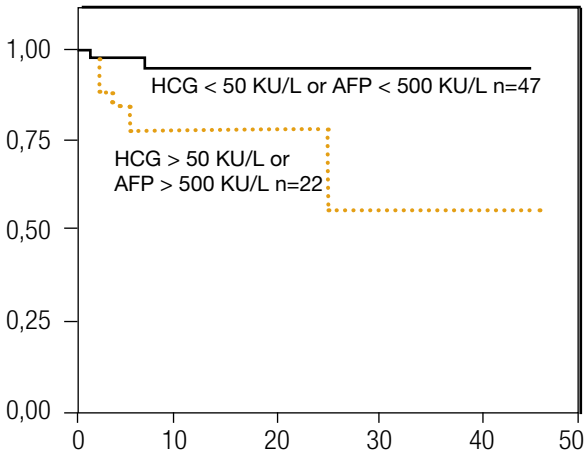

FIG. 2

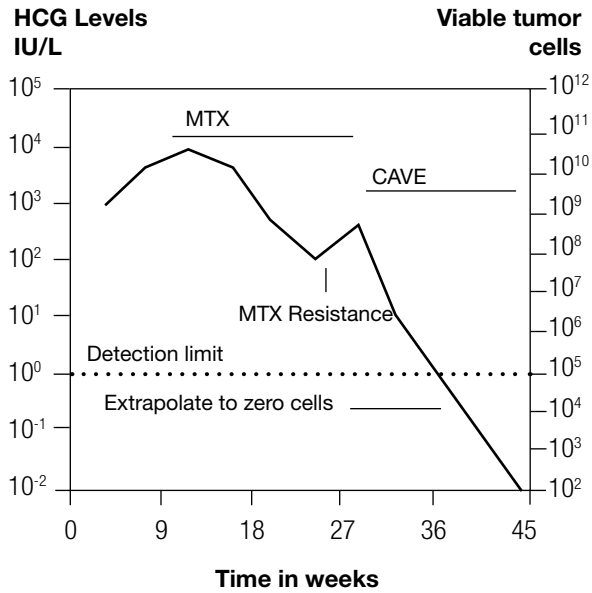

FIG. 3

in a similar way in the in different tumors.

Another example is the use of PSA in the tumor evaluation of prostate cancer:[9] if PSA > 10 ng/ml, the existence of prostate cancer is likely; if PSA > 40 ng/ml, metastatic lymph nodes are likely; if PSA > 100 ng/ml, bone metastases are certainly present.

Also, the HCG level, the measurement of which has been used in the diagnosis and monitoring of the treatment of trophoblastic and some testicular germ-cell tumors, may have prognostic importance. *Fig. 2* shows a chart that lists the serum levels of HCG and a-fetoprotein (AFP) with the prognosis of testicular teratoma.

4 - Evaluation of the response to therapy

It is possible, through the serial determination of the serum levels of tumor markers, to evaluate the tumor response to the initial therapy which, some authors argue, is when tumor markers are more important and show the best results.

This occurs, for example, with the oncofetal protein (CEA), which is a tumor marker for several human cancers, but serum levels of which can also increase in many inflammatory diseases of the digestive tract. The frequency with which CEA level is high, and the value, depend on the magnitude of the disease, its degree of differentiation (> differentiation > production) and the existence of liver metastases. Thus, the primary use of CEA relies on monitoring the response to therapy and the disease progression. The high levels should return to normal after complete resection of the primary tumor, in cases where treatment involves surgery.[6]

Serum levels of lactate dehydrogenase (LDH) are also increased in many malignancies, and the magnitude of this increase, and its subsequent evaluation, are useful measures of antitumoral response.

Again, and with the marker closer to the profile of the ideal marker, a linear relationship between tumor mass and serum hormone can be observed for HCG; this has a prognostic value and is usually reduced after effective treatment.

Fig. 3 shows the response of choriocarcinoma to two types of chemotherapy, using the HCG levels at different times of the treatment as an indicator of the response.[10]

Although a direct relationship between therapeutic response and modification of the tumor marker concentration is not universally accepted, Breastall et al. in 1991, showed a simple way to evaluate tumor response to the treatment. They considered that a tumor has:[10] no response if the marker concentration does not fall below <50% of the concentration before treatment; unlikely response if the marker concentration decreases to 50% that of the previous concentration; a response if the marker concentration

TABLE VI

Evaluation of CEA for malignant non-colorectal tumors

Organ	Percentage
Lung	52–77
Pancreas	61-68
Stomach	40-60
Liver	40-60
Biliary tract	80
Thyroid	50-70
Cervix	42-50
Endometrium	27
Ovary	35
Breast	30-50

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TABLE VII

Serum concentration of alpha-fetoprotein in patients with malignant tumors

Diagnosis	Number of cases included	Percentage of values above 40 ng/mL
Hepatocellular carcinoma	130	72
Testicular teratocarcinoma	101	75
Pancreatic carcinoma	44	23
Gastric carcinoma	91	18
Colon carcinoma	193	5
Bronchial carcinoma	150	7
Breast carcinoma	55	0

is only 10% of that of the pre-treatment concentration; and a complete response if the marker concentration corresponds to the non-malignant reference values after treatment.

5 - Early detection of relapse

For most markers, there is interest in performing determinations at certain time intervals after the initial treatment. This implies close regular and clinical and laboratory follow-up, bearing in mind that when accentuated serum level increases of a marker are observed, these are often associated with local relapse or distant metastasis, occurring some time after clinical identification.

Whether the initial treatment is surgical or chemical (with cytotoxic), serial determination of tumor markers may allow, in many cases, a preview of the effectiveness of the treatment and relapses and/or metastases.

Only once the efficacy of the treatment is certain, reflected by normal or close to normal serum levels of the tumor markers, can we discuss or consider relapses when high levels are found to be again for the same markers in the serum.

In operable tumors, high levels should return to normal after complete resection of the primary tumor, thus ensuring that the treatment has been radical; any subsequent increase of the markers may indicate a relapse. If after surgery, the high levels are persistent or are increasing, then the presence of a residual or recurrent tumor is highly likely.[1]

Likewise, in disseminated tumors, serial monitoring of the tumor markers related to each tumor enables us to discover the evolution of the tumor, i.e. whether it is stable, regressing or progressing; the latter occurs when relapse or local or distant metastases occur.[4]

When monitoring the tumor and for the early detection of relapses, it is also important to consider more than one tumor marker; for example, in breast cancer, CA 15.3 is more sensitive than CEA, and increased serum levels of the marker may occur several months after the clinical diagnosis of metastases.[3]

Limitations of the use of tumor markers

Of all the markers currently in use, the one that is closest to the ideal marker is β HCG. This β subunit of the chronic gonadotropin hormone is usually found in the maternal serum during pregnancy, but it is not found in the serum of non-pregnant women and healthy men under normal conditions.

Its detection in both men and non-pregnant women suggests the existence of a germ-cell tumor, of the testicle or trophoblast, respectively. In pregnant women, very high β HCG levels may be detected (higher than those in the gestation period), which

TABLE VIII

Detection of Antigen CA 125 in the serum

Group	Total number of subjects tested	n (%) Serum concentration	
		>350/mL	>650/mL
Control, disease-free	888	9 (1.0)	2 (0.2)
Males	537	4 (0.7)	2 (0.4)
Females	351	5 (1.4)	0 (0.0)
With benign diseases	143	9 (6.3)	3 (2.1)
With non-gynecological cancer	200	57 (28.5)	44 (22.0)
Pancreatic	29	17 (58.6)	13 (44.8)
Lung	25	8 (32.0)	6 (24.0)
Breast	25	3 (12.0)	2 (8.0)
Colorectal	71	16 (22.5)	12 (16.9)
Gastrointestinal	30	8 (26.7)	6 (20.0)
With ovarian carcinoma	101	83 (82.2)	75 (74.3)

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are useful in the diagnosis of molar pregnancy that can develop into choriocarcinoma.[7]

The existence of a linear relationship is verified between tumor mass and serum HCG, and the latter has a prognostic value.[3] The speed with which it decreases can be used to evaluate therapeutic efficacy, and its recurrence is direct evidence of recurrence of the tumor.[10]

However, most tumor markers meet the requirements included in the definition of an ideal marker. Most tumor markers are not exclusively synthesized by the malignant tumor, or by a single malignant tumor, and can be detected in the serum and other biological fluids, even in the absence of cancer.

Tables VI, VII and VIII show, for example, how different tumors relate to a same marker, thereby limiting the usefulness of most of the markers.

High levels of CEA were observed in non-neoplastic diseases of the intestine, liver, pancreas, kidneys and lungs as well as in collagen diseases and smoking subjects (up to 10 mg/ml in smokers[2]).

The substances considered as tumor markers vary in their origin, biochemical structure, mode of activity and level of intervention in the neoplastic process. The tumor marker concentrations at the peripheral level also depend on several factors,[2,4] which are given below:

1) The number of producing cells, because the tumor marker is generally produced by neoplastic cells and is logical to assume that the greater the number of cells, the greater the synthesis and release into the bloodstream, which depends on the tumor vasculature;

2) The more widespread the tumor vasculature, i.e. the easier it is for a marker to reach the bloodstream, the higher the detectable concentrations, although we cannot conclude, from this positivity, whether it is a case of highly disseminated regional tumor loci or distant metastases. Besides, not all tumor cells have the same synthesis rate, so the tumor biology must be taken into account;

3) The kinetics or tumor growth rate, cell differentiation degree, and cellular changes cause the markers to have different release times, depending on the marker in question. For example, the enzyme markers are released into the circulation mainly during cell necrosis, and are usually associated with tumors with rapid growth and cellular changes. But even for these, the high rates and concentrations found are dependent on the metabolism of the marker;

4) It is therefore important to know which tissues or cell strains are associated with the synthesis and/or degradation of the tumor marker. For example, antigen 125 (CA 125) is segregated by the mesothelial cells of pleura, peritoneum and endometrial tissue, which may be high in cases of high endometriopathy or pathology that directly or indirectly affects the mesothelium and is not necessarily neoplastic.[8] Another example is the antigen associated with squamous carcinomas, particularly in the control of the evolution of malignant epidermoid neoplasms. Its elimination occurs mainly via the urine; therefore, to properly use this marker it is necessary to know the renal function of the patient affected by the neoplasm.[10] The same applies, for example, to the carbohydrate antigen (CA 19.9) with regard to liver function.[1]

5) Changes in the marker metabolism condition its plasma half-life. The mean elimination time of the tumor marker into the bloodstream varies from hours for β HCG to several days for CEA, and this is important information when using the tumor marker to specify the response to treatment.

All these factors must be taken into account when evaluating a marker and interpreting its results.

Conclusions

As one may imagine, the ideal thing would be to have a substance or technique which would be specific enough to indicate the existence of a cancer for all detected anomalies, and sensitive enough to diagnose cancer in its early stages.

Three reasons make this ideal marker difficult to visualize, based on the current state of knowledge: 1) the available markers are not only produced by neoplastic cells; 2) cell heterogeneity in the same cancer which do not always produce the same marker; 3) the antibodies used in the determination techniques are not entirely specific.

Based on the following, and by way of conclusion, it can be said that tumor markers in general do not have, and do not in themselves constitute, diagnostic value. They may, however, be useful as information for prognosis, therapeutic evaluation and control of relapses.[2,3,4,6,7,10]

It is precisely during or after the treatment, whether by surgery, radiation or chemotherapy, that markers are significant.

It is, therefore, essential to determine whether a patient had, prior to treatment, a high marker so that when the patient is evaluated again, the marker concentration can be checked for decrease, reflecting tumor response to the treatment, or increase, as a sign of recurrence.

In fact, in clinical practice the importance of the markers is not only related to the type of tumor, but also to the purpose for which the marker is used.

We should value what it is available to medicine, such sophisticated method as tumor markers, without neglecting common sense in our search for a diagnosis. ■

References

1. Molina R, Ballesta AM. Marcadores tumorais. Jornal do Médico 1991; 130: 662-665.

2. O'Rourke TJ. Tumor markers. In: Calabresi P, Shein PS. – ed. Lit. – Medical Oncology: basic principles and clinical management of cancer. 2nd ed. New York: McGraw – Hill, cop. 1993: 163-172.

3. Monteiro MD Marcadores tumorais: notas sobre a sua utilização na prática clínica. O Médico 1990; 123: 261-276.

4. Piedbois P. Marqueurs Tumoraux: une aide précieuse sons certain conditions. Rev Prat 1993; 7: 27-28.

5. Gamble AR et al. Uso da imunoreactividade dos marcadores tumorais para a identificação da localização primária do cancro metastático. BMJ 1993; 2: 343-347.

6. Bunn Jr, Paul A. Marcadores Tumorais In: CECIL. Tratado de Medicina Int. 19º ed, Rio de Janeiro: Guanabara Koogan, cop. 1993: 1053-1056.

7. Mendelsohn J Princípios básicos de las neoplasias. In: Harrison-Princípios de Medicina Interna. 12º ed. Madrial: Interamericana, McGraw – Hill, cop. 1991; 2: 1839-1841.

8. Webb MJ. Rastreio do cancro do ovário: ainda um longo caminho a percorrer. BMJ 1993; 2: 400-401.

9. Chisholm G, Rana A. Prostate Cancer. The practitioner. Paris, 1992; 236: 610-617.

10. Roulston JE, Leonard RCF. Serological Tumour Markers: an introduction. Edinburgh: Churchill Livingstone. 1993.