**Tumor Markers**

Introduction

A tumor marker is a substance produced by a tumor or by the host in response to a tumor, which is used to differentiate a tumor from normal tissue, or to detect the presence of a tumor based on measurements in the blood or secretions. Such substances are found in cells, tissues, or body fluids and are measured qualitatively or quantitatively by chemical, immunologic, or molecular biological methods.

Morphologically, cancer tissue has been recognized by pathologists as resembling fetal tissue more than normal adult differentiated tissue. Tumors are graded according to their degree of differentiation as:

(1) well differentiated,

(2) poorly differentiated

(3) anaplastic (without form).

Tumor markers are the biochemical or immunologic counterparts of the differentiation state of the tumor. In general, some tumor markers represent re-expression of substances produced normally by embryogenically closely related tissue.

Only few number of tumor markers are specific to one type of cancer; others are seen in several cancer types. Many well-known markers are also seen in noncancerous conditions. Consequently, these tumor markers are not diagnostic for cancer. However, it is thought that the concentration of tumor markers in blood reflects tumor activity and volume.

From the clinical point of view, an ideal tumor marker should be both specific for a given type of cancer and sensitive enough to detect small tumors for early diagnosis or during screening. Unfortunately, few markers are specific for a single individual tumor (tumor-specific markers); most are found with different tumors of the same tissue type (tumor-associated markers).

In clinical practice, the most useful use of current tumor markers is in the evaluation of the progression of disease status after initial therapy and for monitoring subsequent treatment modalities.

Features of an ideal tumor marker

(1) specific production by premalignant or malignant tissue early in the progression of disease.

(2) produced at detectable levels in all patients with a specific malignancy.

(3) expression in an organ site-specific manner.

(4) evidence of presence in bodily fluids obtained noninvasively or in easily accessible tissue.

(5) levels related quantitatively to tumor volume, biological behavior, or disease progression.

(6) relatively short half-life, reflecting temporal changes in tumor burden and response to therapy.

(7) existence of a standardized, reproducible, and validated quantitative assay.

Cancer

A simple definition of cancer is a relatively autonomous growth of tissue. Understanding the cause of autonomous growth would clearly facilitate the search for a cure.

A carcinogen is an agent that causes cancer. A carcinogen may be:

1- physical (e.g., radiation)

2- chemical (e.g., a polycyclic hydrocarbon)

3- biological (e.g., a virus).

Exposure to such an agent may cause cancer by producing direct genotoxic effects on deoxyribonucleic acid (DNA) (e.g., as with radiation) or by increasing cell proliferation (e.g., by a hormone), or both (e.g., through the use of tobacco).

Prostate cancer is the leader among men, and breast cancer is the leader in women, followed by cancer of the lung, colo-rectum, and bladder (men) or uterine corpus (women).

Surprisingly, since the peak death rates from all cancers in 1990 for men and 1991 for women, death rates decreased significantly. This significant rate of decrease supports the conclusion that early detection and more effective treatment combined with prevention (e.g., decreasing smoking, improving diet) could reduce the mortality rate of cancer in the future.

Advances in molecular genetics have resulted in a better understanding of the genesis of human cancer. The proliferation of normal cells is thought to be regulated by growth-promoting oncogenes and counterbalanced by growth-constraining tumor suppressor genes. The development of cancer appears to involve the activation or the altered expression of oncogenes, or the loss or inactivation of a tumor suppressor gene.

The goal is to diagnose cancer when a tumor is still small enough to be completely removed surgically. Unfortunately, most cancers do not produce symptoms until the tumors are too large to be removed surgically, or until cancerous cells have already spread to other tissue (metastasized).

In general, tumor markers are classified into the following categories:

(1) enzymes

(2) hormones

(3) oncofetal antigens

(4) carbohydrate markers

(5) blood group antigens

(6) proteins

(7) receptors

(8) genes

Clinical applications of tumor markers

Despite the many clinical applications of tumor markers in the management of cancer, most of these applications are limited by the variable sensitivity and specificity of each tumor marker.

***Sensitivity: TP/ TP+ FN***

***Specificity: TN/TN+FP***

The two most reliable uses of tumor markers in clinical practice are:

1- Prediction of therapeutic response

Very few known markers have a powerful predicting response to specific therapies.

Example include the steroid hormone receptors for predicting response to antiestrogens in breast cancer.

2- Monitoring the effectiveness of cancer therapy

For patients with advanced disease, who are treated with various modalities, it is important to know if therapy works. In this regard, biomarkers usually provide information that is readily interpretable and more economical, more sensitive, and safer than radiologic or invasive procedures.

In breast cancer, the concentration of markers, such as CA 15-3 or CA 27.29, changes with treatment and the clinical outcome of the patient.

3- Screening for cancer

With the exception of PSA, most cancer markers are not specific for a particular tissue, and elevations may be due to diseases of other tissue, including benign and inflammatory diseases. Thus diagnostic specificity may be low, leading to many false positives.

4- Diagnosing cancer

Surprisingly, tumor markers are of limited use in the diagnosis of cancers, again due to low specificity and sensitivity.

5- Evaluating cancer prognosis

Despite that many tumor markers have prognostic values; their accuracy is not accurate enough to warrant a specific mode of therapy.

7- Tumor staging

As the value of a tumor marker is not significantly related to the size of the tumor, its metastasis, lymph nodes state, or capsular penetration, tumor markers are of limited use in staging of cancer.

8- Localizing tumor and directing radiotherapeutic agents

Only few tumor markers are applicable for this use.

9- Detecting tumor recurrence or remission

Despite the importance of using biomarkers to detect cancer relapse, current markers are limited by the following:

A- In certain groups of patients, biomarkers are not produced and do not detect relapses.

B- Therapies for treating recurrent disease are not effective at present.

C-Sometimes biomarkers provide misleading information (e.g., clinical relapses occur without biomarker elevation, or biomarker is elevated nonspecifically, without progressive disease, leading to overtreatment or discontinuation of a current and successful treatment protocol).

Groups of tumor markers

I- Enzymes

Enzymes are among the first groups of tumor markers that have been discovered. Only few enzymes have enough sensitivity and specificity to be used as a tumor marker.

1- Alkaline phosphatase (ALP)

The alkaline phosphatase in the sera of normal adults comes primarily from the liver. As a tumor marker, ALP is elevated in:

1- primary or secondary liver cancer

2- bony metastasis (prostate or breast cancer)

2- Lactate Dehydrogenase (LDH)

LDH is an intracellular enzyme released to the circulation in case of cell damage. Elevation of LDH in malignancy is rather nonspecific. It has been demonstrated in a variety of cancers, including liver cancer, non- Hodgkin’s lymphoma, acute leukemia.

3- PSA

Prostate cancer is the leading cancer in older men. It is potentially curable by radical prostatectomy when detected early (organ confined). Therefore, early detection is important and PSA is widely used for this purpose. It is considered one of the most promising tumor markers available.

PSA exists in two major forms in blood circulation, the free form and the protein bound form.

Clinical Applications of PSA

PSA is an extremely useful tumor marker and is used to detect and monitor treatment of prostate cancer.

*A- Screening and Early Detection of Prostate Cancer*

*B- Monitoring Treatment*

**II- Hormones**

The production of hormones in cancer involves two separate routes.

First, the endocrine tissue that normally produces it can produce excess amounts of a hormone. Second, a hormone may be produced at a distant site by a nonendocrine tissue that normally does not produce the hormone. The latter condition is called *ectopic syndrome*.

Examples of hormones used as tumor markers include:

1- Calcitonin

Calcitonin is a polypeptide with 32 amino acids produced by C cells of the thyroid. Normally, it secreted in response to increased serum calcium, inhibits the release of calcium from bone and thus lowers the serum calcium concentration. Its concentration is elevated in medullary carcinoma of the thyroid.

2- Human Chorionic Gonadotropin (hCG)

Basically, hCGis used for diagnosis and monitoring pregnancy. It is a useful tumor marker for tumors of the placenta (trophoblastic tumors) and for some tumors of the testes.

Clinical Applications

The upper reference limit in men and nonpregnant women is 5.0 IU/L.

-Patients with trophoblastic tumors typically have elevated concentrations of hCG (>1 million IU/L).

-It is also elevated in 70% of those with nonseminomatous testicular germ cell tumors, and less frequently in those with seminoma.

III- Oncofetal antigens

Oncofetal antigens are proteins produced during fetal life. These proteins are present in high concentration in the sera of fetuses and decrease to low concentration or disappear after birth.

In cancer patients, these proteins often reappear, revealing that certain genes are reactivated as the result of the malignant transformation of cells.

1- α-Fetoprotein (AFP)

AFP is a marker for hepatocellular and germ cell (nonseminoma) carcinoma.

Clinical Applications

- AFP is physiologically elevated during pregnancy, started at the 12th week of gestation reaching its peak at the 14th week.

- Significant elevation of AFP occurs in hepatocellular carcinoma (HCC).

- Minimal elevation is seen in early HCC, hepatitis, or liver cirrhosis.

2- Carcinoembryonic antigen (CEA)

CEA is a marker for colorectal, gastrointestinal, lung, and breast carcinoma, but because of significant false positive and false negative results it is not used for screening. CEA testing may be useful as an adjunct to clinical staging. Persistently elevated concentrations that are 5 to 10 times the upper reference limit strongly suggest the presence of colon cancer.

After successful initial therapy, CEA concentrations decline. Rising CEA concentrations may indicate recurrence of disease. The lead time from CEA elevation to clinical recurrence is about 5 months.

IV- Carbohydrate markers

Carbohydrate-related tumor markers may be:

(1) antigens on the tumor cell surface.

(2) secreted by the tumor cells.

The most important examples of this group of tumor markers are:

1- CA 125 Ovarian, endometrial

2- CA 15-3 Breast, ovarian

V- PROTEINS

Several proteins, other than enzymes and hormones, can be used as tumor markers with various sensitivity and specificity.

1- Immunoglobulin

Monoclonal immunoglobulin has been used as a marker for multiple myeloma. Monoclonal paraproteins appear as sharp bands in the globulin region of serum electrophoretic patterns.

More than 95% of patients with multiple myeloma have such an electrophoretic pattern. Appearance of nonmalignant monoclonal immunoglobulins increases with age, reaching 5% in patients older than 75 years. Bence Jones protein is a free monoclonal immunoglobulin light chain in the urine.

The concentration of monoclonal immunoglobulin at initial diagnosis is a prognostic indicator of disease progression.



**Diagnostic criteria of multiple myeloma**

* M-protein in serum: IgG ≥3 g/dL, IgA >1 g/dL ***or***
* Bence-Jones protein >1 g/24h ***and/or***
* Bone marrow clonal plasma cells ≥10%
* Signs of end organ damage:

 Calcium >11.5 mg/dL (>2.65 mmol/L)

 Creatinine >2 mg/dL (177 μmol/L or more)

 Hemoglobin <10 g/dL or 2 g/dL <normal (<12.5 mmol/L<normal)

 Lytic or osteopenic bone disease

VI- Receptors

Estrogen and progesterone receptors

Estrogen and progesterone receptors are used in breast cancer as indicators for hormonal therapy. Patients with positive estrogen and progesterone receptors tend to respond to hormonal treatment. Those with negative receptors will be treated using other therapies, such as chemotherapy. Hormone receptors also serve as prognostic factors in breast cancer. Patients positive for hormone receptors tend to survive longer.

ERs and PRs are routinely measured in all newly diagnosed breast cancers. Of patients with carcinoma of the breast, 60% have tumors that are ER positive. The greater the ER content of the tumor, the higher the response rate to endocrine therapy.

The PR assay is a useful adjunct to the assay of ERs. Indeed, metastatic breast cancer patients with both ER- and PR-positive tumors have a response rate of 75% to endocrine therapy, whereas those with ER-positive and PR-negative tumors have a 40% response rate.

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