Tumor markers: an overview

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Abstract:
Tumor markers are biochemical substances elaborated by tumor cells, due to either the cause or effect of malignant process. These markers can be normal endogenous products that are produced at a greater rate in cancer cells or the products of newly switched on genes that remain quiescent in the normal cells. A tumor marker is produced by the tumor and when present in significant amounts, indicates the presence of a cancer.

Key words: Tumor, marker, biochemical, malignant.

Introduction:

Tumor markers are biochemical substances elaborated by tumor cells due to either the cause or effect of malignant process. These markers can be normal endogenous products that are produced at a greater rate in cancer cells or the products of newly switched on genes that remain quiescent in the normal cells.

A tumor marker produced by the tumor and when present in significant amounts, indicates the presence of a cancer. They may be present as intracellular substances in tissues or may be released into the circulation and appear in serum [1].

Tumor markers can be broadly classified as:

1. Oncofetal antigens e.g. Alpha-fetoprotein (AFP), Carcinoembryonic antigen (CEA).
2. Tumor associated antigens/Cancer antigens e.g. CA125, CA19-9.
3. Hormones e.g. Beta human chorionic gonadotropin, Calcitonin.
4. Hormone receptors e.g. Estrogen& progesterone receptors.
   Enzymes and isoenzymes eg Prostate specific antigen (PSA), Neuron specific enolase (NSE).
5. Serum and tissue proteins e.g. Beta2 microglobulin, S-100.
6. Other biomolecules e.g. Polyamines.

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Quantitative and qualitative evaluation of these markers is possible through modern techniques of sensitive immunoassays (RIA and ELISA)\textsuperscript{[1]}. 

Some of the clinically relevant tumor markers:

**Alpha-feto protein (AFP):**

This is a major protein of fetal serum, but is usually undetectable after birth. AFP elevations are associated with hepatocellular carcinoma and non-seminomatous germcell tumors. AFP levels are abnormal in 80% patients with hepatocellular carcinoma and exceed 1000 ng per mL in 40% patients with this cancer. Other GITract cancers occasionally cause elevation of AFP, rarely to greater than 1000ng per mL. Patients with cirrhosis or viral hepatitis may have abnormal AFP values, although usually less than 500ng per ml. Pregnancy also is associated with elevated AFP levels, particularly if the pregnancy is complicated by a spinal cord defect or other abnormality. Where AFP levels are elevated, but no abnormality is found there is a greater level of obstetric risk\textsuperscript{[2]}.

**Beta human chorionic gonadotopin (b-hCG):**

This is normally produced by the placenta. Elevated b-hCG levels are most commonly associated with Pregnancy, Germ cell tumors and Gestational trophoblastic disease. False positive levels occur in hypogonadal states and with marijuana use. Patients with AFP and bhCG levels that do not decline as expected after treatment, have a significantly worse prognosis, and changes in the therapy should be considered. Tumor markers are followed every one to two months for one year after treatment, then quarterly for one year, and less frequently thereafter. AFP or bhCG elevation is frequently the first evidence of germ cell tumor recurrence\textsuperscript{[2]}.

**Prostate specific antigen:**

The positive predictive value of PSA levels in prostate cancer greater than 4 ng/mL is 20-30%. This rises to 50% when PSA levels exceed 10 ng/mL. Nevertheless, 20-30% of men with prostate cancer have PSA levels within normal ranges. Fewer than 2% of men with PSA levels below 20 ng/mL have bone metastases from prostate cancer\textsuperscript{[2]}.

**Cancer antigen 19-9:**

Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers, but may also be raised in colorectal, gastric, hepatocellular, oesophageal and ovarian cancers. It has a sensitivity and specificity of 80-90% for pancreatic cancer. It has a sensitivity of 60-70% for biliary tract cancer. Benign conditions such as cirrhosis, cholestasis, cholangitis and pancreatitis also result in elevations, although values are usually less than 1,000 units per ml. It may also be raised in diabetes mellitus and irritable bowel syndrome. CA 19-9 levels above 1,000 units per ml predict the presence of metastatic disease.

Lack of sensitivity and specificity restrict the use of CA 19-9 measurement in the early diagnosis of pancreatic cancer but it may complement other diagnostic procedures, especially in the absence of cholestasis\textsuperscript{[2,3]}.

**Microphthalmia transcription factor:**

Microphthalmia transcription factor (Mitt) is important in melanocyte development and melanoma growth. It has been investigated regarding its expression as a marker for circulating melanoma cells in blood and to determine the correlation with disease stage and survival in melanoma patients. It can detect subclinical metastatic disease and predict treatment outcome in melanoma patients\textsuperscript{[2]}.
Circulating methylated DNA:

Circulating nucleic acids may be biomarkers that could be used in the early detection of cancer. They could also be used to follow the progression of patients with cancer. Methylated DNA is one such nucleic acid-based marker. DNA is a very stable molecule and can be detected using simple polymerase chain reaction-based approaches[2].

Carcinoembryonic Antigen (CEA):

Carcinoembryonic antigen (CEA) is a glycoprotein, which is present in normal mucosal cells but increased amounts are associated with adenocarcinoma, especially colorectal cancer. CEA therefore has a role as a tumour marker. Levels exceeding 10 pg/L are rarely due to benign disease[2].

Cancer Antigen 125 (CA-125):

This is a glycoprotein normally expressed in coelomic epithelium during fetal development. This epithelium lines body cavities and envelopes the ovaries. Elevated CA 125 values, most often are associated with epithelial ovarian cancer, although levels also can be increased in other malignancies. Levels are elevated in about 85% women with ovarian cancer, but in only 50% those with stage I disease.

Low sensitivity limits its usefulness in ovarian cancer screening. The positive predictive value is only 20 percent, translating to five exploratory laparotomies for each ovarian cancer diagnosed. Also, survival was not improved in the women who were found through CA 125 screening to have ovarian cancer.

Higher levels are associated with increasing bulk of disease and are highest in tumours with nonmucinous histology. Multiple benign disorders also are associated with CA 125 elevations, presumably by stimulation of the serosal surfaces. In postmenopausal women with asymptomatic palpable pelvic masses, CA 125 levels higher than 65 units per mL have a positive predictive value of 98 percent for ovarian cancer. Levels can also be used in assessing function in chronic heart failure[2].

In combination with other diagnostic methods, tumor markers play an important role in the diagnostic process and in treatment planning. Besides, by combining various tumor markers we can achieve a greater specificity and sensitivity in the follow up of one type of malignancy. The simplicity and noninvasiveness of the method for the determination of tumor markers enables monitoring the disease also in the patients, not eligible for other types of diagnostic procedures.

On account of individual differences in the serum concentrations of each individual tumor marker, we recommend multiple determinations of tumor markers and monitoring the dynamics of serum concentrations (even in cases when serum concentrations are below the cutoff values).

It would be ideal to determine the level of tumor markers in each patient before treatment, several times between the treatment (depending upon the type of treatment, type of malignancy, and the sort of tumor marker), and after the treatment. Tumor markers should be monitored also, for a certain period after the treatment has been finished, best at regular control examinations (once in six months or once yearly), This kind of follow up will enable a timely detection of disease recurrence even in asymptomatic patients.

From a single determination of tumor markers we can find out whether the malignancy has developed or not and, if it has, what is its extent, but only if the concentrations are very high[4].
References: