Tumor Markers in breast Cancer

By

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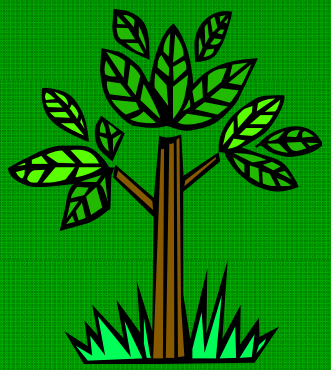

What are Tumor Markers ?

A tumor marker is a substance found in the blood, urine, or body tissues that can be elevated in cancer, among other tissue types. There are many different tumor markers, each indicative of a particular disease process, and they are used in oncology to help detect the presence of cancer. An elevated level of a tumor marker can indicate cancer; .however, there can also be other causes of the elevation

They are synthesized and released by cancer cells or produced by the host in response to the presence of tumor

Potential Uses of Tumor Markers

- Risk identification
- Screening
- Aiding diagnosis
- Assessing prognosis
- Predicting response to therapy
- Predicting severe toxicity due to therapy
- Postoperative surveillance and
- Monitoring therapy in advanced disease

Classification

-Tumor specific proteins

-Non-specific proteins or markers related to malignant cells

-Cell specific proteins overexpressed in malignant cells

Tumor Specific Proteins

Expressed only in tumor cells

Example: an oncogene is translocated and fused to an active promoter of another gene → fusion proteins → constant active production → development of malignant clone

Philadelphia chromosome in CML, t(9;22) (q34;q11) bcr/abl translocation

Non-Specific Proteins or Markers Related to Malignant Cells

Oncofetal proteins：expressed by cells as they de-differentiate and take on embryonic characteristics

α-FP：HCC, testicular, ovarian cancer

CEA：many GI tumors

Cell Specific Proteins Overexpressed in Malignant Cells

Proteins expressed normally by differentiated cells, but are expressed at higher rates in the corresponding tumor cells

PSA : prostate cancer

In vivo Factors that affect TMs

1-Elevated values may be observed in *renal failure and cholestasis*, due to impaired excretion of the markers.

2. In *rheumatic diseases*, elevated levels of CA19-9 are observed.

3. Drug interactions: *antiandrogens* inhibit PSA production.

4. Rectal examination or transuretheral manipulation result in elevation of the serum level of PAP and PSA.

5. Cigarette smoking can result in elevation of CEA levels up to 10 ng/mL.

Factors (in addition to malignant disease) that affect serum concentrations of tumor markers

False positive results

- presence of inflammatory processes;
- benign liver diseases and disturbancies in metabolism and excretion (AFP, TPA, CEA, CA 19-9, CA 15-3);
- disturbancies of renal function (beta-2-microglobulin, calcitonin, PSA, CEA, CA 19-9, CA 15-3);
- extensive tumor necrosis;
- as a consequence of diagnostic and therapeutic procedures (digitorectal examination, mamography, surgery, radio and chemotherapy);
- as a consequence of different physiological conditions (pregnancy - ßHCG, AFP…..).

Tumor Markers in breast cancer

1-SERUM TUMOR MARKERS

Numerous serum tumor markers has been studied :

-MUC-1 family: CA 15.3, MCA, CA 549, CA 27.29, CAM 26, CAM 29

- CEA

- Oncoproteins (C-erbB-2)

-glycolitic enzymes: LDH...

-Milk proteins: lactoalbumin.

- cytokeratins: TPA.

MUC-1 antigens : The most widely used. Similar sensitivities and specificities

The use of more than one MUC-1 antigen is unlikely to confer any advantage.

CEA measurement can provide additional complementary nformation.

One MUC-1 tumor marker and CEA

TUMOR MARKERS IN LOCALIZED BREAST CANCER

Tumor Marker determination may complement patient staging:

CA 15.3 and CEA are related to tumor burden, with significantly higher values in node positive patients and in patients with larger tumors.

Preoperatively elevated levels of either CA 15.3 or CEA are associated with adverse outcome

However, Most studies with large patient groups and long follow-up times conclude that pre-operative serum CA 15.3 and CEA concentrations are independent prognostic factors.

Early detection of metastases.

Increases in CA15.3 provide the first indication of recurrence, prior to clinical or radiological indication, in 40-55% of patients.

-Additional CEA measurements can increase the sensitivity in the early detection of recurrence obtained with CA 15.3 by up to 5-25% ,Lead Time 2-18 months (mean 5.2 month)

Specificity for the detection of recurrence: related to the cut-point used

CEA > 5 ng/ml : 5% of false positive results

CA 15.3 > 35 U/ml: 6,5% of false positive results

Using higher cut-off values (CA 15.3 60 U/ml, CEA 10 ng/ml) and at least two serial increases (>15%), specificity increased to almost 100%.

ADVANCED DISEASE

Tumor marker sensitivity is significantly higher than in loco-regional disease.

-Combination of several markers (CA15.3, CEA, cytokeratins) increase the sensitivity to 90% in patients with distant metastases.

-Tumor marker sensitivity is related to the site of metastases

THERAPY MONITORING

The most important clinical application: Monitoring therapy response.

Patients in remission usually have decreasing marker levels, while those with progressive disease generally have increasing levels.

Biochemical changes often precede clinical or radiological signs of response or progression, potentially enabling earlier treatment decisions regarding continuation of ineffective therapy, change of therapy...

Tumor markers should be measured prior to every chemotherapy course and at least three monthly for patients receiving hormone therapy.

An increase in tumor marker concentration of at least 25% of the previous value, with the second value above the reference interval, to be significant, recommending that such an increase be confirmed in a second specimen obtained within a month. If the continued increase is confirmed, this provides evidence of progressive disease. Similarly, confirmed decreases in serum levels of more than 50% are consistent with tumor response.

2- tissue tumor marker

-Utility: Prognosis and predict response to therapy.

-Most useful: Hormone receptors (ER, PR), oncoproteins (HER-2 or CerbB-2 or *neu)*

ER AND PR AS MARKER TUMOR

-ER and PR are transcriptional factors which mediate the actions of estrogens and progesterone, respectively.

Both receptors are now known to exist in 2 different forms, ER-alpha and useful when deciding on adjuvant hormone treatment

Not guarantee response, fails in 30~40% of patients to endocrine treatment

As diagnostic marker when it is a primary unknown tumor

Assay of hormone receptors is mandatory in the selection of patients with both, early and advanced breast cancer for treatment with hormone therapy

HER-2 (c-erbB-2, *neu)*

Oncogene present in chromosome 17 that encode a 185 kDa

•Gene amplified or overexpressed in 20-30% invasive breast cancers

It has been suggested that HER-2 over-expression is associated with relative resistance to hormone therapy, adjuvant CMF therapy, but there are still conflicting reports.

Similar situation, controversy also exists on the association between overexpression and response to anthracycline- ased adjuvant therapy.

- **BRCA1 gene on chromosome 17q**：familial breast-ovarian cancer syndrome, and breast cancer in early-onset breast cancer families → **high risk screening**

Cancer	Marker(s)	Recommended use
Breast	CEA, CA 15-3	M
Carcinoid	5-HIAA	D
Hepatoma	AFP	S, D, P, M
	CEA	M
Gastrointestinal*	CEA	P, M
	CA 19-9	
Ovary	CA 125	P, M
	CASA	P, M
Prostate	PSA	D, P, M
	PAP	P, M
Germ-cell tumours	AFP	D, P, M
	BHCG	D, P, M
	LDH	P, M
	PLAP (seminoma)	P, M
Choriocarcinoma	BHCG	D, P, M
Thyroid	Thyroglobulin	S, M
Neuroblastoma	VMA	D, P, M
	Catecholamines	D, P, M
	NSE	M
Myeloma	Immunoglobulins	D, P

D, diagnosis; P, prognosis; S, screening; M, monitoring course of disease or response to therapy.
*Colorectal, stomach and pancreatic carcinomas.

Disease	Marker	Marker in use				Marker still at experimental stage
		Screening	Detection and diagnosis	Staging and prognosis	Follow up	
Colon cancer	Carcinoembryonic antigen			(X)	X	
Breast cancer	Oestrogen receptor			X		
	CA15.3			X	X	X
	CA27.29					X
	Her-2/neu			X		X
Prostate cancer	Prostate specific antigen	(X)			X	
Ovarian cancer	CA125		X		X	
	CA19.9 (CA74.2)					X
Thyroid cancer	Thyroglobulin		X		X	
	Calcitonin		X		X	
Testicular cancer	Human chorionic gonadotrophin		X		X	
	α Fetoprotein		X		X	
Sarcoma:						
Synovial sarcoma	t(X;18)		X		X	
Ewing's sarcoma	t(11;22)		X			
Alveolar rhabdomyosarcoma	t(2;13)		X			
Granolytic sarcoma	t((9;11)		X			
Myxoid liposarcoma	t(12;16)		X			
Round cell liposarcoma	t(12;16)		X			
Congenital fibrosarcoma	t(2;15)		X			
Clear cell sarcoma	t(12;22)		X			
Dermatofibrosarcoma protuberans	t(17;22)		X			
Melanoma	Tyrosinase		X			
Adrenal carcinoma	Steroids		X			
	Catecholamines		X			
Lymphoma	t(8;14)		X		X	X
	t(11;14)		X		X	X
	t(2;5)		X		X	X
	t(3;14)		X		X	X
	sCD25					X
	sCD44					X
Leukaemia	Numerous cytogenetic alterations		X		X	

(X)=occasional use (prostate specific antigen) or possible future use (carcinoembryonic antigen).

Conclusion

Screening：

most tumor markers fail, because

1. Low prevalence of malignancy in asymptomatic persons
2. Not elevated in patients with small-volume (early) cancer

Diagnosis：

most markers have low specificity, only for high risk groups (αFP, β-HCG , PSA, thyrocalcitonin)

Prognosis：

markers correlate with tumor burden

Monitor treatment response：

most markers' level alone cannot be used to define CR (except: β-HCG in trophoblastic malignancy)

Early detection of recurrence

Thank you for your attention!