Original Article

Clinical Significance of Tumour Markers

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ABSTRACT

Tumour markers are biochemical indicators of the presence of a tumour, which are selectively produced by the neoplastic tissue and released into blood or in other body fluids. They are widely accepted and applied to the management of patients with cancer since the introduction of diagnostic immunopathology. Tumour markers include oncofetal antigens (AFP), glycoproteins (CEA), placental proteins (PLAP), hormones (ACTH and HCG), enzymes (PSA and PAP) and other molecular species. Monoclonal antibody technique is the most commonly used method for identification of specific marker in tissue, urine or blood sample. Assay of various tumour markers can be used for population screening, tumour detection, diagnosis, staging, prognosis, or follow up of malignant diseases.

Keywords: Cancer, Immunopathology, Monoclonal antibody, Oncofetal antigen, Placental protein.

INTRODUCTION

During the last four decades, since the introduction of diagnostic immunopathology, tumour markers have been widely accepted and applied to the management of patients with cancer. In recent years definition of tumour marker has been expanded to include, in addition to those markers circulating in blood, marker measured either quantitatively or qualitatively in tissue and in other body fluids including urine and cerebrospinal fluid and even the assay of genes and oncogenes[1].

The term "tumour marker" embraces a spectrum of molecules of widely divergent characteristics, but sharing an association with malignancy that facilitates their application in the clinical detection (diagnosis, screening) and management (monitoring, prognosis) of cancer patients[2].

Classically, tumour markers are synthesized by malignant cells or certain benign condition and released into the blood stream; however, markers may be produced by host tissues in response to direct invasion or metabolic changes induced by the tumour[3]. They are generally not diagnostic, although they can provide information that may contribute to the diagnostic process. They could be used for population screening

and for detection, diagnosis, staging, prognosis, or follow up of malignant diseases[4]. Most commonly, antibodies are used to identify the presence of specific tumour marker in tissue, urine or blood samples[5].

Tumour markers are biochemical indicators of the presence of a tumour. They include cell surface antigen, cytoplasmic proteins, enzymes and hormones. Tumour marker can not be construed as primary modalities for the diagnosis of cancer. Their main utility in clinical medicine has been as a laboratory test to support the diagnosis[6].

The ultimate goal is to develop a test to detect cancer in its early stages, while treatment is most effective and complete cure is more reasonably attainable. Development of a cost effective and simple method to gain additional information to improve the management of cancer patients is the primary objective in the development of tumour marker assays[7].

An ideal tumour marker as described by Chin Loy *et al.*[8] should be:

- Detectable only when malignancy is present.
- Specific for the type and site of malignancy.
- Correlates with the amount of malignant tissue present.
- Responds rapidly to a change in tumour size.
- Easy and cheap to measure, from a laboratory point of view.

However, at present, no ideal tumour marker fulfills all of the above criteria to satisfy various clinical applications with adequate sensitivity and specificity[3].

Tumour marker classification

Class I (Tumour specific protein)

A specific tumour marker is expressed only in tumour cells. These antigens are unique to a neoplasm not shared by other tumour of same histological type. Extensive work carried out recently using various experimental model systems has revealed that many chemically induced tumours express private or unique antigens not shared by other histologically identical tumour induced by the same chemical even in the same animal[9]. The best example is the so called fusion proteins associated with malignant process in which an oncogene is translocated and fuse to an active promoter of another gene[4]. The result is a constantly active production of the fusion protein, leading to the development of a malignant clone. The Philadelphia chromosome in chronic myeloid leukemia is best-known example[10]. These mechanisms frequently occur in hematological malignancies but also in some tumour of mesodermal origin[11].

Class II (Non-specific proteins or markers related to malignant cells)

Most tumour antigens are not unique (specific) to the individual tumour. In fact, they are expressed by many tumour of a specific histological type and of other histological type, but not expressed by normal adult tissue. Oncofetal antigen, or embryonic antigens are non-specific proteins and less stringent but still very useful. These are expressed in cells during embryological development and in cancer cells. The two best examples of oncofetal antigens are alpha-foeto protein, and carcino-embryonic antigen (CEA). The CEA is expressed in all gastrointestinal tumour as well as in many other tumour[12] where as alpha fetoprotein is used to diagnose hepatocellular cancer but is also expressed in testicular and ovarian cancer[13].

Class III (Differential- specific proteins)

Some antigens are expressed by both cancer and normal adult tissue. Differential specific proteins are expressed normally by differentiated cells but are expressed at higher

rates (over-expressed) in the corresponding tumour cells, which is why a relative increase in serum concentration can be used as tumour marker; this is the case with prostate specific antigen concentration in prostate cancer[14]. Cell specific proteins are used for diagnostic purpose for example, the tyrosinase protein expressed in melanocytes in malignant melanoma[15]. Differential specific protein antigens also serve as useful differentiation marker in the diagnosis of lymphoid and prostatic cancer in animals and human beings[9].

Types of tumour marker

There are three major types of tumour markers that are released into the circulation and measured. Tumour marker types usually in blood specimen, are summarized in the following table 1[6].

Evaluation of tumour marker assay

The diagnostic value of a tumour marker depends on the prevalence of the disease in the population group being considered. To evaluate the performance of a tumour marker assay for use in clinical situation such as detection, monitoring, prognosis or diagnosis of disease, various statistical factors such as the sensitivity, specificity and positive & negative predictive values are necessary if the assay is to be considered clinically valid[2].

Sensitivity

The sensitivity of a test is defined as the ability of the test to detect those individuals with cancer in the test population. The greater the sensitivity, the fewer the false-negatives.

Specificity

The specificity of a test is defined as the ability of the test to identify those free from cancer in the test population. The greater the specificity, the fewer the false positives.

Positive predictive value

The positive predictive value is defined as the measure of the validity of a positive test, or in other words, the proportion of positive tests that are true positive cases.

Negative predictive value

The negative predictive value is defined as the measure of the validity of a negative test, or, the proportion of negative tests that are true negative cases.

Common methods used to identify tumour marker

Monoclonal antibodies technique

Traditionally, monoclonal antibodies technique is commonly used method to identify tumour marker proteins[5]. Tumour marker assays are developed using monoclonal antibodies to detect tumour antigen present in blood or other body fluid. The tumour marker detection system can be based on a radioactive label (RIA) or an enzyme based reaction (E1A).

- An R1A or radio immuno assay refers to techniques used to detect and quantify the presence of tumour antigens in patient's blood. The assay is based on a "Sandwich" technique using a radio-labeled antibody as a "detector" and a "capture" antibody bound to a solid phase substrate or bead. Generally, a patient's blood specimen is added to each well of a microtiter plate and incubated for a given time period. The plate is then washed and the units of tumour antigen remaining in the well are determined based on comparison to standard known levels of antigen[32].
- An EIA or enzyme-linked immunoassay can be produced in a manual assay format or automated format. An enzyme label or tag is used for the detection system and linked to an antibody which detects the amount of antigen present in patient's

blood. The resulting colorimetric reaction is measured using a microplate reader. The antigen levels present in patient's blood are compared to known quantities of antigen in the assay standards[33].

Tumour marker assays are produced in an automated format to enable the laboratory to perform a large number of test in a reproducible and cost-effective manner. Automated assays generally utilize an enzyme-based detection system as in the manual format assays. Manual format kits generally use microtiter plate with wells where the reaction occurs.

A technical example

Mammary tumours are the most common neoplasias of female dogs and may have complex histological pattern[16]. TAAs (Tumour Associated Antigens) is an example of a tumour marker in sera of canine mammary carcinoma patient. SB_2 is a murine monoclonal antibody (MAb) generated against a canine mammary carcinoma cell line by immunizing laboratory mice with a cell line derived from canine mammary carcinoma cell which circulates in the patients with mammary carcinoma[17]. SB_2 were used in a competitive ELISA to measure TAAs in canine serum samples. Then serum TAAs concentration measured by EIA and correlated with the patient's disease status or response following surgical resection or chemotherapy. The upper limit of normal TAAs concentration in disease-free dog is 20 IU (Inhibitory Unit) with MAbs SB_2. It is found that TAAs- positive sera were significantly greater among the dogs with mammary carcinoma[17].

Reversed transcriptase and polymerase chain reaction (RT-PCR)

Reverse Transcriptase and Polymerase Chain Reaction is used to study very small amount of gene expression and has been shown to be a much more sensitive method for detecting mictrometastasis[18]. Amplification by PCR allows detection of transcripts from a single tumour cell among 10 to 100 million normal cells. The success of marker depends on its specificity and sensitivity. In many solid tumours the use of specific markers is often limited, because the heterogeneity of disease leads to most marker being expressed in only a small proportion of the tumour[4]. Reverse Transcriptase and Polymerase chain Reaction (RT-PCR) was first used to show the bcr/abl translocation in patients with chronic myeloid leukaemia in 1988[19], but has now been used experimentally for detecting micrometastases in a wide variety of malignant diseases[18].

Immunohistochemistry

Techniques of immunohistochemistry can be used directly on tumour for prognostic and diagnostic purpose, as is done in melanoma, bone cancer and liver carcinoma[4]. The proliferative potential of canine osteosarcomas (OSs) and chondrosarcomas (CSs) was evaluated immunohistochemically by Labeling Ki-67 antigen with MIB-1 antibody (proliferative marker) and found high MIB-1 positive index (MIB-1 PI) which supports the view that OSs are clinically more aggressive than CSs in dogs[20]. The use of immunohistochemical staining methods has been demonstrated for analysing the expression of some tumour markers in routinely processed tissue samples for canine liver carcinoma and suggest that some of the tumour markers *e.g.* Keratins are correlated with histological type of Tumour[21].

Apart from immunohistochemical staining, SDS-PAGE and western blot analysis were used to demonstrate that HSP (Heat shock Protein) 60 and 70 as a potential marker for canine transmissible venereal tumour (CTVT)[22].

The clinical significance of tumour marker

Tumour marker can be used in a variety of situations to aid in the management of cancer patients[8].

1. For screening and diagnosis of cancer.
2. To monitor the effectiveness of therapy.
3. For detection of early recurrence.
4. For differential diagnosis.
5. As prognostic and predictive indicators.

Screening

Screening is different from diagnosis in that it attempts to identify a disease or condition at an early stage prior to the appearance of clinical symptoms. It is the systematic application of a test to identify individuals at sufficient risk of a specific disorder, and who haven't sought prior medical attention for that disorder, to enable them to benefit from further investigation or direct preventive action. The PSA test for prostate cancer is an example of a tumor marker assay that has been clinically accepted for screening purposes[23]. Other screening tests are the Pap test for cervical cancer, and the FOBT or fecal occult blood test for colorectal cancer[24]. The optimal characteristics of a screening test include ease of performance, clinical acceptability, low cost, high sensitivity and specificity, and positive and negative predictive values.

Diagnosis of cancer

A tumour marker assay used for the detection of cancer should have the following qualities:

- Easy to perform.
- Having low cost.
- Acceptable to patient.

Such a diagnostic test is designed to identify asymptomatic individuals with a high likelihood of having the cancer. In evaluating such a test, one looks at its ability to detect early stage disease.

To monitor the effectiveness of therapy

To determine the effectiveness of therapy during the course of treatment following surgery it is essential to determine a patient's response to therapy. The main treatments for cancer are chemotherapy, hormone therapy, surgery and radiotherapy. It is important to determine if the treatment a patient is receiving is providing its intended effect. The most common use of tumour markers is for monitoring a patient's response to therapy. The CA 19-9 assay is used to monitor a pancreatic cancer patient's response to therapy[26], and the CA 15-3 assay is used to monitor a breast cancer patient's response to therapy. Increased concentration of AFP in the serum is indicative of canine multicentric lymphoma and of value in assessing the extent of neoplastic infiltration of liver[27].

For pre-treatment tumour marker measurement in patients with suspected malignancy, clinical presentation will usually suggest as to which markers may be most helpful (Table-3).

Determining recurrence of the tumour

At the completion of primary chemotherapy, a tumour marker assay can be used to determine the persistence of malignancy. An elevated marker level may indicate the presence of a tumour, although a low level does not necessarily mean that no tumour is present.

Tumour markers can be used serially to determine recurrences. Obtaining a base line level, the patient is followed serially. A rising level is indicative of recurrence and the increase often precedes clinical or radiographic determination. A therapeutic decision can be made prior to extensive recurrences of the cancer therefore, in some cases more expensive investigation (*e.g.* diagnostic imaging) can be avoided. CA 125 is an example of a tumour marker test that can be used to aid in detection of residual ovarian carcinoma in patients who have completed

their first line of therapy[28]. The marker can be used in this case to reduce the patient's need for diagnostic second-look surgical procedures.

Differential diagnosis

The gold standard for the diagnosis of cancer is histopathological examination of tumour tissue obtained during biopsy or surgery. But histological procedures are not always conclusive, therefore often requiring additional testing for definitive results. Tumour marker is helpful in differential diagnosis (*e.g.* in germ cell cancer where they may be different cell types) and especially where there are metastatic deposites but the primary site is unknown *e.g.* Neuron specific enolase (NSE) used in differential diagnosis of lung cancer, CA 15.3 in breast cancer[2]. PLAP (Plancental Alkaline Posphatase) differentiate the source of tumour among liver, bone and germ cell origin; non-diagnostic by itself, it helps to confirm malignancy in a small number of patient[3].

It can also be used to aid in differentiating malignant from benign disease, in the diagnosis of metastatic cancer of unknown origin, and with conventional imaging tests in difficult diagnostic cases. Tumour marker can be used to help distinguish tumour type and origin as well as distinguish primary from metastatic tumours.

Tumour marker as prognostic indicator

The traditional methods used for assessing a patient's prognosis for outcome and disease management are determination of tumour size, grade, and lymph node status. Tumour markers can be used in addition to other methods to forecast a patient's response to therapy, thereby enabling the physician to appropriately adjust or determine the level of treatment needed to manage disease.

Bladder cancer is an example of a disease of canines that would benefit from a prognostic marker. Because dogs with bladder cancer often have advanced disease at the time of diagnosis, the identification and use of a tumour marker that could facilitate earlier diagnosis is a valid approach to improve prognosis. Commercially available ELISA test kit to quantitate basic fibroblast growth factor (bFGF) in the urine of dog is used. In normal dog the urine bFGF concentration was 2.23 ng/g creatinine whereas there was significantly higher urine bFGF concentration i.e. 9.86 ng/g creatinine[29]. So there is a need to find a prognostic marker to differentiate patients with significant, aggressive cancer from those with innocuous cancer to determine appropriate treatments.

Tumour marker as predictive indicators

Tumour markers can be used to predict a patient's response to a given therapy or outcome. Although postoperative chemotherapy in treatment of cancer appears to have reached the limit of cytoreduction, this may be due to nonselective administration of chemotherapeutic agents rather than attainment of the true limit of cytoreduction. Therefore some patients receive therapy with little benefit, while they suffer from serious side effects.

Molecular profile of Tumour cells may determine tumour response to chemotherapy, and therefore the selective use of chemotherapy based on prediction will ultimately provide a cure for mammary tumour[30]. Hence, tumour marker can be used as "predictive indicator" to predict a patient's response to a given chemotherapy or outcome.

An example of a tumour marker used as a predictive indicator is Estrogen Receptor (ER) Status[31]. ER levels are determined in women diagnosed with breast cancer for predicting their response to hormone therapy and assisting in the choice of appropriate therapy. ER negative patients rarely respond to hormone therapy, while 60% of ER

positive patients do respond to hormone therapy. ASCO (American Society of Clinical Oncology) has recommended that the ER assay can be performed on all patients diagnosed with breast cancer.

Limitation of Tumour Marker Assay

Measurements of tumour marker level can be useful when used along with history, physical examination and radiographic procedures to detect, monitor and determine recurrence in some types of cancer. However, measurements of tumour marker levels alone are not sufficient to diagnose cancer for several reasons[3].

- Tumour marker levels can be elevated in benign conditions.
- Tumour marker levels are not elevated in every cancer patient.
- Many current tumour markers are not specific to a particular type of cancer
- The level of a tumour marker can be raised by more than one type of cancer.

Hence, no ideal tumour marker currently exists to satisfy all clinical application with adequate sensitivity and specificity.

CONCLUSION

Increasing interest in implementing the practice of diagnostic immunopathology in oncology has encouraged the extensive research on tumour marker for cancer diagnosis and management. Tumour markers are proteins associated with malignancy and released into blood or in other body fluids. These are broadly classified into three classes depending on the specificity of protein markers produced by malignant cells or by host tissue in response to metabolic changes induced by the tumour itself. Apart from MAbs technique, RT-PCR and immunohistochemistry are commonly used methods in various tumour marker assays. The diagnostic values of these assays depend on the prevalence of the disease in the population and on sensitivity and specificity of the marker being used. Current tumour markers include oncofetal antigens (AFP), glycoproteins (CEA), placental proteins, hormones, enzymes and other molecular species.

Appropriate use of serum marker facilitates an evidence-based approach to medicine in cancer therapy. Tumour marker tests are generally, not diagnostic, but they help along the road to diagnose by providing information that contribute to confirmatory diagnosis. In fact, there are only few markers, which are of use in screening and diagnosis of tumours or in determining prognosis. If a tumour marker has been found to be raised in serum in a patient who has had a tumour diagnosed histologically then the tumour marker is useful in monitoring response to therapy and detection of early recurrence.

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Table 1. Nature of tumour marker

Nature of tumour marker	Example
Enzyme	• Prostate-specific antigen (PSA; a serine protease) • Prostatic acid phosphatase (PAP) • Creatinekinase • Alkaline phosphatase
Hormone	• Human chronic gonadotropin (HCG) • Calcitonin • Adrenocorticotrophic hormone (ACTH) • Ectopic hormone (HCG, GH, GnRH & Renin)
Glycoprotein	• Oncofetal antigen (Alpha fetoprotein and carcinoembryonic Antigen) • Tissue polypeptide antigen (TPA) Tissue polypeptide specific antigen (TPS)
Mucins and other glycoprotein	• Breast cancer Antigen CA 15-3 • Ovarian cancer Antigen CA 125 • Colorectal & Pancreatic Cancer Antigen CA 19-9

Table 2. The following are some of the major tumour markers and the cancer they are associated with (Sturgeon, 2002)[25]

Cancer	Tumour marker
Breast / mammary	Glycoprotein CA15-3 (BR-MA)
Ovarian	Glycoprotein CA125 (OM-MA)
Prostatic	Prostate-specific antigen (PSA) Prostatic acid phosphatase (PAP) Creatine kinase
Pancreatic Gastrointestinal	Glycoprotein CA19-9 (GI-MA)
Colorectal Gastroitestinal Lung Breast / mammary	Carcinoembryonic antigen (CEA)
Liver Testicular	Alpha-Fetoprotein (AFP)
Placenta (trophoblastic tumours) Testicular	Human chorionic gonadotropin (HCG)
Thyroid	Thyroglobulin (TG)
Medullary thyroid (C-cells)	Calcitonin
Canine Transmissible Venereal Tumor (CTVT)	Heat shock protein 60, HSP 70
Miscellaneous	Cytokeratin 18 Tissue polypeptide (specific) antigen (TPS)

Table 3. Characteristics of tumour markers[2]

Tumour markers	Biochemical properties	Molecular weight	Primary clinical applications
Alpha-fetoprotein (AFP)	Glycoprotein, 4% carbohydrate; considerable homology with albumin	~70 kD	Diagnosis and monitoring of primary hepatocellular carcinoma and germ cell tumours. Prognosis of germ cell tumours. Canine multicentric lymphoma.
Cancer antigen 125 (CA125)	Mucin identified by monoclonal antibodies	~200 kD	Monitoring ovarian carcinoma. Prognosis after chemotherapy.
Cancer antigen 15.3 (CA15.3, BR 27.29)	Mucin identified by monoclonal antibodies	>250 kD	Monitoring breast cancer
Cancer antigen 19.9 (CA19.9)	Glycolipid carrying the Lewis[a] blood group determinant	~1,000 kD	Monitoring pancreatic carcinoma
Carcinoembryonic antigen (CEA)	Family of glycoproteins, 45-60% carbohydrate	~180 kD	Monitoring gastrointestinal and other adenocarcinomas

CYFRA 21-1	Fragments of cytokeratin 19	~30 kD	Monitoring bladder and lung carcinoma.
Estrogen receptor	Nuclear transcription factor	65 kD	Predicting response to endocrine therapy in breast cancer.
Tumour markers	Biochemical properties	Molecular weight	Primary clinical applications
Human chorionic gonadotrophin (hCG)	Glycoprotein hormone consisting of two non-covalently bound subunits	~36 kD	Diagnosis and monitoring non-seminomatous germ cell tumours, choriocarcinomas, hydatidiform moles, seminomas. Prognosis of germ cell tumours.
Neuron specific enolase (NSE)	Dimer of the enzyme enolase	~87 kD	Monitoring small cell lung carcinoma, neuroblastoma, apudoma
Placental alkaline phosphatase (PLAP)	Heat-stable isoenzyme of alkaline phosphatase	~86 kD	Monitoring of germ cell tumours (seminomas)
Progesterone receptor	Nuclear transcription factor	A form: 94 kD B form: 120 kD	Predicting response to endocrine therapy in breast cancer.
Prostate specific antigen (PSA)	Glycoprotein serine protease	~36 kD	Diagnosis, screening and monitoring prostatic carcinoma
Squamous cell carcinoma antigen (SCC)	Glycoprotein sub-fraction of tumour antigen T4	48 kD	Monitoring squamous cell carcinomas
Tissue polypeptide antigen (TPA)	Fragments of cytokeratin 8, 18 and 19	~22 kD	Monitoring bladder and lung carcinoma
Tissue polypeptide specific antigen (TPS)	Fragment of cytokeratins 18	~22 kD	Monitoring metastatic breast carcinoma