RESEARCH COMMUNICATION

Comparison of Serum Tumor Associated Material (TAM) with Conventional Biomarkers in Cancer Patients

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Abstract

Objective: To compare expression level of serum tumor associated materials (TAM) with several conventional serum tumor biomarkers, eg., carcinoembryonic antigen (CEA), carbohydrate antigen19-9 (CA19-9), carbohydrate antigen 15-3 (CA15-3), alpha-fetoprotein(AFP), in selected solid tumors. Methods: Patients diagnosed histologically or cytologically with liver, breast, esophageal, gastric, colorectal or pancreatic cancers were enrolled into this study. After diagnosis, the level of TAM was determined by chemical colorimetry, and levels of conventional tumor markers was measured by chemiluminescence methods. Results: A total of 560 patients were enrolled into this study. No statistically significant difference was detected in TAM and the above mentioned tumor biomarkers in terms of their positivity and negativity (P>0. 05). Conclusions: Detection of TAM in liver, breast, esophageal, gastric, colorectal, and pancreatic cancer patients demonstrates a good accordance with CEA, CA199, CA153, and AFP, thus suggesting that further study is warranted to verify whether TAM could be a surrogate for these conventional biomarkers.

Keywords: Tumor asscociated material - TAM - tumor marker - cancer

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Introduction

Carcinoembryonicantigen (CEA) is one of the most widely used tumor markers worldwide. Its main application is mostly in gastrointestinal cancers, especially in colorectal malignancy (Duffy, 2001). CEA was first described in 1965 by Gold and Freedman (Gold et al., 1965), when they identified an antigen that was present in colon adenocarcinoma but that appeared to be absent from healthy adult colon. Because the protein was detected in only cancer and embryonic tissue, it was given the name carcinoembryonic antigen, or CEA. Subsequent work showed that CEA, or at least a CEA-like molecule, was also present in certain healthy tissues, although concentrations in tumors were on average 60-fold higher than in the nonmalignant tissues (Boucher et al., 1989).

The relationship between biomarker and pancreas cancer is less clear. The best established marker is CA 19-9 which is a sialylated Lewis antigen of the MUC1 protein with an overall sensitivity of 80% and specificity of 90% in detection of pancreas cancer (Steinberg, 1990). Unfortunately, CA 19-9 may be positive in patients with non malignant diseases including cirrhosis, chronic pancreatitis, cholangitis, as well as other gastrointestinal cancers (Duffy et al., 2010). Patients with certain blood types are incapable of expressing the antigen recognized by CA 19-9 (Steinberg,1990). Furthermore, only 65% of those with resectable pancreas cancer have elevated CA 19-9 levels (Goggins, 2005). Nonetheless, CA 19-9 is widely used to evaluate patients with suspected pancreas cancer and those undergoing treatment.

Alpha-fetoprotein (AFP), a 70 kD glycoprotein synthesized from fetal yolk sac, liver and intestines, has a half-life of 5-7 days. Total serum AFP level is a prognostic indicator of the response and survival of germ cell tumors (Fujiyama et al., 2002). However when AFP level is slightly increased it may be falsely elevated owing to nonneoplastic liver disease. Although total AFP is a useful serological marker for diagnosis of HCC, the false-negative or -positive rate with AFP level alone may be as high as 40%, especially for its early diagnosis or detection of small size HCC (< 3 cm) (Yao et al., 2000). It could be very diffcult to make a distinction between tumors and falsely elevated AFP levels because of benign liver diseases. Recently the separation of a hepatoma-specifc AFP subfraction has been reported to be superior

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to total AFP level in both sensitivity and specifcity in differentiating between benign and malignant liver disease (Khien et al., 2001; Wu et al., 2006).

In breast cancer, however, the role of serum markers is less well established. The most widely used serum markers are CA15-3 and CEA (Bosl et al., 1977). The potential uses of serum markers in breast cancer include aiding early diagnosis, determining prognosis, prospectively predicting response or resistance to specific therapies, surveillance after primary surgery, and monitoring therapy in patients with advanced disease (Duffy, 2006).

Serum tumor associated material (TAM) testing kit was a new test kit, developed by QINGDAO BO-XING Biotechnology Co., Ltd, can be quickly and easily used for cancer early detection, screening, and monitoring the efficacy of cancer treatment.

Detection of serum TAM by a special polymer carrier to identify a specific oligosaccharide sequence to identify specific glycan terminal epitope (eg, Lewis oligosaccharides X (sLex), etc.), the end of the sialic acid, and with the reactions. At present most used tumor markers are glycoproteins, glycolipids, oligosaccharides contain specific sequences, TAM polymer carrier identified by the sequence of these oligosaccharides with a variety of markers to achieve the reaction. TAM removed most of the macromolecular protein complex (at 450 nm can color in the non-tumor-related material) that could affect the test results by sedimentation centrifuge, to make accurate of the test results (Serum tumor associated material (TAM) testing kit, QINGDAO BO-XING Biotechnology Co., Ltd).

Altered glycosylation patterns are a hallmark of the tumor phenotype. Meezan et al in 1969 first described with the demonstration that healthy fibroblasts have smaller membrane glycoproteins than their transformed counterparts (Meezan et al., 1969). This finding was later corroborated with histological evidence that lectins show differential binding to healthy compared with malignant tissue (Turner, 1992; Saussez et al., 1998).

In addition to changes in the corestructures of glycans, altered terminal structures are also associated with malignancy. Glycosyltransferases (for example, sialyltransferases and fucosyltransferases) involved in linking terminating residues on glycans tend to be overexpressed in tumour tissue.The increase in activity of these glycosyltransferases in turn leads to the overexpression of certain terminal glycans. Examples of terminal glycan epitopes commonly found on transformed cells include sialyl Lewis x (sLex), sialyl Tn (sTn), Globo H, Lewis y (Ley) and polysialic acid (prostate-specific antigen, PSA) (Gabius., 1988; Sell, 1990; Taylor-Papadimitriou et al., 1994; Hakomori et al., 1997). Many of these epitopes are observed in malignant tissues throughout the body, including the brain, breast, colon and prostate (Orntoft et al., 1999).

Another common feature of tumors is the overproduction of certain glycoproteins and glycolipids. For example, epithelial tumors often overproduce mucin glycoproteins, which are characterized by dense clusters of O-linked glycans. Mucins are used as diagnostic markers of cancer and can also function as scaffolds for most of the above-listed cancer-associated epitopes (Hollingsworth et al., 2004).Additionally, cancer tissues can display an increase in ganglioside expression. For example, complex gangliosides (for example, GD2, GD3 and fucosyl GM1) are found at elevated levels in small-cell lung cancers, neuroblastomas and melanomas (Hakomori et al., 1997; Hakomori, 2000). Although gross changes in glycosylation of tumor tissues are apparent, no single change seems to distinctly differentiate normal and malignant cells. Instead, each type of malignant tissue is characterized by a distinct set of changes in glycan expression (Zhang et al., 1997).

Glycan changes that indicate malignancy can be used for diagnosis. Indeed, the commonly used 'CEA' test for colon cancer monitors serum levels of an antibody specific for a cancer-associated glycan (sLea) (MacDonald, 1999). Glycan analyses of other serum markers, such as CA125 (Kui Wong et al., 2003)and prostate-specific antigen (Basu et al., 2003; Peracaula et al., 2003), reveal distinct changes in glycosylation in ovarian and prostate tumour tissue, respectively. These studies suggest that specific changes in glycosylation could be useful as diagnostic tools. For many cancers, however, there are no serum markers available.

The aim of this study was to compare the expression of serum tumor associated materials (TAM) with other common tumor markers, eg., CEA, CA19-9, CA15-3 and AFP.

Materials and Methods

To be included in the study, patients who were hospital inpatients had to have histologically confirmed malignant tumors,and blood collected. General information about research and clinical work conducted in Jiangsu Cancer Hospital and Research Institute has been described elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Yan et al., 2011; Yu et al., 2012; Gong et al., 2012; Zhang et al., 2012).The Characteristics of patients are presented in Table 1.

Measured by fasting blood 2ml, separation of serum, -20 °C to save, backup. Strict accordance with the clinical serum tumor associated materials (TAM) detection kit operating requirements. In the colorimetric under 450 nm, calculated measured value.According QINGDAO BO-XING Biotechnology Co., Ltd provides criteria: TAM detection value ≥ 95 U/ml demonstrates positive, < 95 U/ml negative (Serum tumor associated material (TAM) testing kit, QINGDAO BO-XING Biotechnology Co., Ltd).

Table 1. Characteristics of the Patients

	N	Male	Female	Age (Median)	TAM (Average)
Liver cancer	30	25	5	58	102.9291
Pancreatic cancer	20	11	9	58	103.6023
Colorectal cancer	89	55	34	55	98.09137
Gastric cancer	161	118	43	60	98.47871
Esophageal cancer	109	89	20	62	98.90658
Breast cancer	151	0	151	52	95.80002

TAM, serum tumor associated material.

Table 2. TAM and CEA, AFP, CA19-9, CA15-3 in Cancer Patients

	Positive (%)	Negative (%)	P Value (Chi-square)
Liver cancer			
TAM	14 (46.7)	16 (53.3)	1.000(Fisher's exact)
AFP	5 (16.7)	25 (83.3)	
Pancreatic cancer			
TAM	13 (65)	7 (35)	1.000(Fisher's exact)
CA19-9	4 (20)	16 (80)	
Colorectal cancer			
TAM	40 (44.9)	49 (55.1)	0.127
CEA	41 (46.1)	48 (53.9)	
Gastric cancer			
TAM	73 (45.3)	88 (54.7)	0.522
CEA	64 (39.8)	97 (60.2)	
Esophageal cancer			
TAM	56 (51.4)	53 (48.6)	0.663
CEA	45 (41.3)	64 (58.7)	
Breast cancer			
TAM	65 (43.0)	86 (57.0)	0.345
CEA	70 (46.4)	81 (53.6)	
TAM	41 (39.8)	62 (60.2)	0.770
CA15-3	19 (18.4)	84 (81.6)	

CEA, carcinoembryonic antigen; CA, carbohydrate antigen; AFP, alpha-fetoprotein; TAM, serum tumor associated material

The common tumor markers such as CEA, AFP, CA19-9, CA15-3 were measured by chemiluminescence method. If CEA < 3.5 ng/mL, it is defined as negative, AFP < 7 ng/mL negative, CA19-9 < 39 U/mL negative, CA15-3 < 25 U/mL negative.

Statistical analysis

Continuous variables were summarized by descriptive statistics, categorical variables by frequency. Count data by Chi-square test; measurement data as mean ± standard deviation. $P < 0.05$ was considered statistically signifcant. The study data was analyzed through the STATA 8.0 software (Stata Corporation, 4905 Lakeway Drive College Station, Texas 77845 USA).

Results

From April 1st to July 31st 2011,there were totally 560 patients enrolled in this study, men 298,women 262. There was no statistically significant difference in TAM and common tumor markers such as CEA, CA19-9, CA15-3 and AFP in cancer patients (Table 2).

Discussion

About 85% of cancer patients with elevated serum sialic acid, serum saliva acid changes in the level of disease was positively correlated with cancer, continued to rise indicated a poor prognosis. In tumor recurrence or metastasis, the serum sialic acid content increased may be several weeks before the clinical diagnosis, which was significant for early detection and promptly treatment.The elevation level of hydroxyproline,bone and collagen's catabolin, indicated of bone metastases, especially bone metastases of breast cancer. Liu et al., showed that the serum free hydroxyproline in patients with malignant bone tumors were significantly high; peptide with hydroxyproline can identify malignant and benign bone tumors (Liu et al., 1986).

Serum tumor associated material (TAM) is a glycoprotein detection kit, substances such as glucosamine and L-hydroxyproline and other amino acids as the main detected objects. Sialic acid and other glycosaminoglycans substances are the main materials which constitute glycolipids and glycoproteins, closely relating with intercellular adhesion, contact, inhibition of cancerous cells,tumor metastasis and proliferation (Serum tumor associated material (TAM) testing kit, QINGDAO BO-XING Biotechnology Co., Ltd). As the reagent for sialic acid and hydroxyproline and other tumor-related substances were detected at the same time, color overlay, and thus improve the detection sensitivity.

In our study, there was no statistically significant difference in TAM and common tumor markers such as CEA, CA19-9, CA15-3, AFP, etc. Furthermore, TAM removed most of the macromolecular protein complex (at 450nm can color in the non-tumor-related material) that could affect the test results by sedimentation centrifuge, to make accurate of the test results. So that, it can detect more tumor marker in serum sample. Jiang et al showed that TAM was higher in malignant tumors than benign tumors and healthy people (Jiang et al., 2010). We had compared TAM and other common tumor makers in monitoring treatment efficacy in non-small cell lung cancer, found that the level of TAM decreased after chemotherapy compared with before chemotherapy when CT or MRI scan showed disease control, in contrary, it increased when disease progressed, and there was no statistically significant difference in monitoring of TAM and common tumor markers such as CEA, CA125, CA19-9 ($P>0.05$) (Li et al., 2012).

Since the detection of glycosamine substances also composed of the body's immune response protein, Zou et al found that patients with autoimmune disease's positive rate of up to 47.62%, significantly higher (Zou et al., 2004), so the identification of clinical applications should be noted .

In conclusion, detection of TAM in liver, breast, esophageal, gastric, colorectal, and pancreatic cancer patients demonstrates a good accordance with CEA, CA199, CA153, and AFP, thus suggests further study is needed to verify whether TAM could be a surrogate for these conventional biomarkers.

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