Symposium

Symposium on Diagnosis and Treatment of Cancer. Recent Progress*

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I. Diagnosis

1. Tumor Marker

(1) Main Topics of Tumor Marker

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MAIN TOPICS OF TUMOR MARKERS

Since the development of monoclonal antibody technique, so many kinds of new markers were reported. It is impossible to describe all results of recent progress of tumor markers. So, I shall focus our data limiting on tumor markers of the liver of the bile duct and of the pancreas.

The discovery of alpha-fetoprotein (AFP) by Aberev was an impetus to the active recent tumor marker research. AFP is not strictly specific to hepatocellular carcinoma (HCC), because it is detected frequently in low titers in hepatitis and in liver cirrhosis. AFP is a kind of glycoprotein. Lectin binding assay were done by some Japanese workers using Con A, LCA and E-PHA. Using the

difference of reactivities between AFP with lectin, hepatocellular AFP could be differentiated from another kinds of AFP. This is a rather attractive research field. Sawabu et al and Kojima et al reported hepatocellular carcinoma specific novel γ -GTP isoenzyme. Variant alkaline phosphatase reported by Warnock is rather specific in HCC, but not highly positive. In 1984, Liebman et al reported the appearance of HCC specific abnormal prothrombin, PIVKA-II. In Japan, Motohara et al reported their data of abnormal prothrombin from the standpoint of blood coagulation abnormalities. His group could establish an enzyme linked immunoassay (EIA) of PIVKA-II. Fig. I shows my group data of PIVKA-II. The positive rate of PIVKA-II was 58% in HCC, 3% in chronic

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1. Tumor Marker (1)

	0.13	0.25	0.5	1.0	2.0	4.0	8.0	Positive Rate (%)
H C C n=55	•••••	•••••	•••••	•••••	•••••	•••••	•••••	56
L C n=40	•••••	•						3
C H n=35	•••••	•						3
A H n= 5	•							0
F H n= 2	•							0
P B C n=14	•••••	•	•	•	•			29
M L C n=12	•••••	•						9
M C n=18	•••••					•		6
Control n=30	•••••							0

Fig. 1. Value of PIVKA-II in malignant and Benign Diseases (E-1023)

- HCC   hepatocellular carcinoma
- LC   liver cirrhosis
- CH   chronic hepatitis
- FH   fulminant hepatitis
- PBC   primary biliary cirrhosis
- MLC   metastatic liver cancer
- MC   miscellaneous cancer
- E-1023   EIA for PIVKA-II
- PIVKA-II   protein induced by vitamin K absnece or antagonist-II

hepatitis, 3% in liver cirrhosis, 29% in primary biliary cirrhosis, 12% in liver metastasis, 6% in miscellaneous cancer. In obstructive jaundice, intrahepatic or extrahepatic, PIVKA-II could be found because of vitamin-K deficiency. The typical example of intrahepatic obstructive jaundice is primary biliary cirrhosis and that of extrahepatic cause is cancer of the head of the pancreas. PIVKA-II is very specific tumor marker of HCC. It is much more specific for HCC than AFP. In differential diagnosis of HCC from chronic hepati-

Fig. 2. Correlation between PIVKA-II and AFP

Fig. 3. Relationship between size of hepatocellular carcinoma and value of PIVKA-II

tis and liver cirrhosis, PIVKA-II and AFP were shown. There was no relationship between these two tumor markers (Fig. 2). The determination of PIVKA-II is useful in detection of HCC with low or normal AFP titer when the cut-off value of AFP is 200 ng/ml and that of PIVKA is 0.1 arbitrary unit/ml, 74.5% of cases of HCC could be detected by use of these two tumor markers. Fig. 3 shows relationship between size of tumor of HCC and value of PIVKA II. From this figure, PIVKA-II is usually positive when size of tumor is more than 3 cm in diameter. But, very recently, a case of HCC of tumor size of 2 cm in diameter shows 0.11 arbitrary unit/ml. And so, rarely PIVKA-II is positive in small liver cancer. In obstructive jaundice with serum total bilirubin more than 5mg/dl, PIVKA-II is sometimes positive. Several kinds of tumor markers of HCC exist as shown in above mentioned results. The selection of combination of these tumor markers is now being very important for detection of HCC. HCC is usually detected in the clinical follow-up period of chronic hepatitis or liver cirrhosis. These two diseases, especially liver cirrhosis are high risk group of HCC. From this standpoint, AFP and PIVKA-II are the most important tumor markers in HCC.

The most important success of tumor markers in recent years is the discovery of CA19-9 by Koprowski (1979). Another splendid tumor marker of cancer of the pancreas is DU-PAN-2 reported by Metzgar (1982). Value of DU-PAN-2 in the cases of gastrointestinal cancers are investigated. In cancer of the pancreas, DU-PAN-2 is positive in 50% of cases. DU-PAN is also highly

positive in cases of cancer of the liver and of the bile duct. But DU-PAN-2 is frequently positive in cases of acute hepatitis, chronic active hepatitis and decompensated liver cirrhosis. From stage-II cancer of the pancreas, DU-PAN-2 is already highly positive. The correlation coefficient of DU-PAN-2 and CA19-9 in cases of cancer of the pancreas and of the bile duct is 0.334. CA125 was reported by Bast in 1983 as very useful tumor marker of cancer of the ovary. But the positive rate of CA125 is also high in cases of cancer of the liver, of the bile duct, of the pancreas and of the lung. The correlation coefficient between CA125 and CA19-9 in cases of cancer of the pancreas is 0.183. So, CA19-9, DU-PAN-2 and CA125 are tumor markers of cancer of the pancreas. But these three markers are not so specific. Another kinds of tumor markers exist. The typical one is CEA. CEA is frequently positive in cases of any kind of cancer.

One of the most important role of tumor markers is monitoring function of effect of cancer therapy. Another important role of tumor markers are monitoring of progression of disease and judge of prognosis. Users of tumor markers seek clinical usefulness according to their purpose. Tumor marker with less evaluable type will disappear without any active use.

In the past, we have mainly utilized the quantitative value of tumor markers in patient sera. However, recently, immunohistological study of tumor marker localization in tissues are developing. This is very important area of tumor markers

in research. Also investigation of tumor markers in cultured cancer cell line is becoming rather popular. The progress of research in tumor markers has two important area. The one is discovery of new tumor markers in cancer patient sera. The number of recently found tumor markers in this area is increasing in number so quickly.

The other new field of tumor marker research is rather different from the first one. These new field was born from progress of basic cancer research. These are enzymes, hormones, sugar chain compounds, blood group substances, oncogenes, cancer growth factors, oncogenic virus nucleic acids and so on. For example, many oncogenes were detected in HCC. *c-abl*, *c-fes*, *c-fms*, *c-Ha-ras*, *c-ki-ras*, *c-sis*, *c-myc* could be recognized by my group in human HCC cell line, PLC6PRF/5. Hepatitis B virus is oncogenic or not? This is still not completely decided. But using Southern dot hybridization method, hepatitis B virus dna was found in DNA structure of cultured HCC cell line. This fact is named as integration of DNA. In the past, we did not think that these were tumor markers. So, the definition of tumor marker is changing so quickly and the field of tumor marker is enlarging with surprising speed. I think that nowadays tumor marker covers almost all biochemical substances of cancer cells.

The application of tumor markers in recent years has two new approach. The one is imaging diagnosis of cancer and the other is so-called "missile therapy". These two areas are investigating by very limited number of workers.

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(2) Cancer-associated Carbohydrate Antigens

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Antigens defined by monoclonal antibodies raised against human cancers were roughly classified into four groups, a) oncofetal antigen b) cancer-associated carbohydrate antigen c) differentiation antigen and d) growth factor receptor.

Among these, cancer-associated carbohydrate antigens are successfully used as markers for serological diagnosis and treatment of human cancers. It is well known that dramatic changes of carbohydrate chains including incomplete synthesis