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Changes in the plasma abnormal prothrombin level following treatment of hepatocellular carcinoma*

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Summary. The Hokkaido Liver Cancer Study Group focused on the changes in PIVKA-II levels observed in 61 HCC patients after several regimens of treatment in comparison with the AFP levels and the pathophysiological characteristics of HCC. The overall positivity rate for PIVKA-II was 47%, and there was no correlation between the PIVKA-II values and the AFP levels. Accordingly, the HCC detection rate was increased by about 20% by the measurement of both markers. In all, 13 patients underwent hepatic resection, and nonsurgical therapy was carried out in the other 48 subjects. Of the 6 surgically treated patients, 5 (83%) showed a fall in PIVKA-II levels to the normal range immediately after surgery, whereas 14/29 (48%) subjects receiving nonsurgical treatment showed a decrease in PIVKA-II values. Although inconsistency between these tumor markers was detected in four treated cases, we concluded that assay for both of these two parameters may expand their clinical utility for the diagnosis of HCC and monitoring of patients after treatment.

Introduction

The serum AFP level has routinely been used as a tumor marker for hepatocellular carcinoma (HCC), and it has made a substantial contribution to the early detection of HCC and to monitoring of patients after treatment. However, according to the ninth report of the Japan Liver Cancer Study Group (1986–1987), an AFP level of less than 20 ng/ml was found in 27.6% of HCC patients, and in another 27.4% of cases, the AFP value ranged from 21 to 200 ng/ml. Furthermore, AFP measurement proved to be a useful posttreatment monitoring indicator in only 25% of the subjects.

In 1984, Liebman et al. [3] reported that the levels of an abnormal type of prothrombin (des-γ-carboxyprothrombin, a protein induced by vitamin K absence or antagonist, factor 2, PIVKA-II) were significantly increased in the serum of HCC patients. Since then, PIVKA-II has been given considerable attention as a new tumor marker for HCC. Further studies have also demonstrated that the level of PIVKA-II does not correlate with the serum AFP value. Several reports have indicated that PIVKA-II is useful in screening for HCC, but changes in this marker following the treatment of HCC have not been sufficiently investigated.

In the present investigation, the Hokkaido Liver Cancer Study Group focused on the changes in PIVKA-II levels observed in HCC patients after several regimens of treatment in comparison with the AFP levels and the pathophysiological characteristics of HCC.

Patients and methods

A total of 61 HCC patients were entered in this study, and 49 of them had underlying liver cirrhosis. The other characteristics of these patients are summarized in Table 1. In all, 13 patients underwent hepatic resection, and nonsurgical therapy was carried out in the other 48 subjects (Table 2). Transcatheter arterial embolization (TAE) with Adriamycin (ADM) or Farmorubicin (FARM) plus lipiodol followed by Gelfoam was performed in 25 patients, and 12 other subjects received percutaneous ethanol injection therapy (PEIT). A combination of TAE and PEIT was given to 4 patients, and intermittent hepatic arterial infusion therapy with ADM (10–20 mg) or FARM (20–60 mg) delivered via an injection capsule was performed in 7 patients.

Blood samples for the analysis of PIVKA-II and AFP levels were collected before and after treatment at weekly intervals. The plasma level of PIVKA-II was measured by ELISA (E-kit, Eisai Laboratories, Tokyo, Japan). On the basis of measurements of the normal plasma PIVKA-II level, in this series the cutoff value was set at less than 0.1 arbitrary unit (AU)/ml. The AFP levels were simultaneously measured using a radioimmunoassay kit. In this study, the level indicating positivity for AFP was set at above 200 ng/ml.

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Table 1. Characteristics of the 61 patients entered in this study

	Number of cases
Sex (M/F):	
M	49
F	12
Age (years):	
≤40	1
41–50	2
51–60	21
61–70	23
≥70	14
Cirrhosis:	
(–)	9
(+)	49
HBsAg:	
(–)	27
(+)	31
Tumor size (cm):	
≤ 2.0	8
2.1– 5.0	25
5.1–10.0	13
≥10.1	14
AFP (ng/ml):	
≤ 200	32
201– 1,000	15
1,001–10,000	12
≥10,001	2
PIVKA-II (AU/ml):	
≤0.06	32
0.1–1.0	17
1.1–2.0	4
2.1–3.0	1
≥3.1	7

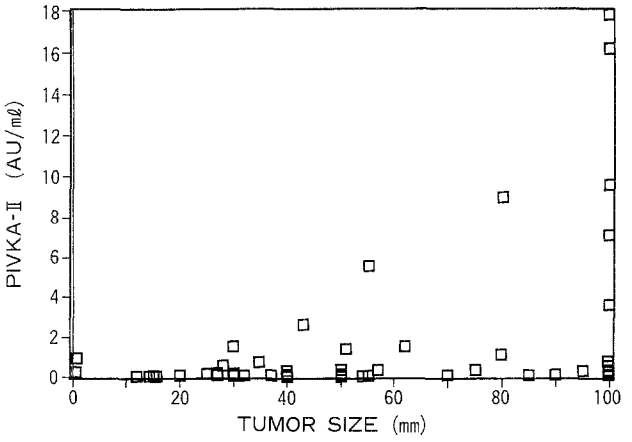

Fig. 1. Relationship between the tumor size and the PIVKA-II level

Results

Pretreatment PIVKA-II and AFP levels

PIVKA-II was positive in 29/61 patients (47%), and 12 of these subjects had AFP levels of less than 200 ng/ml. A total of 30 patients (49%) showed AFP values of more than 200 ng/ml, and 12 (40%) of them had PIVKA-II levels of less than 0.1 AU/ml. In 17 of the 61 patients (28%), both PIVKA-II and AFP were positive. These results indicate that simultaneous measurement of the plasma PIVKA-II and AFP levels should increase the positivity rate for HCC tumor markers by about 20% above that for a single tumor marker. No apparent relationship was found between these tumor markers and the presence of liver cirrhosis or HBs antigen marker. However, all eight small tumors (<2.0 cm in diameter) showed a PIVKA-II value of <0.1 AU/ml (Table 3, Fig. 1), although three were positive for AFP.

Table 2. PIVKA-II and AFP levels in the various treatment groups

		TAE	PEIT	TAE+PEIT	AI	Resection	Total
Number of patients		25	12	4	7	13	61
PIVKA-II (AU/ml)							
< 0.1		15	8	2	0	7	32
≧0.1		10	4	2	7	6	29 (47%)
AFP (ng/ml)							
< 200		15	6	0	1	9	31
≧200		10	6	4	6	4	30 (49%)
PIVKA-II	AFP						
(–)	(–)	11	5	0	0	4	20 (32%)
(–)	(+)	4	3	2	0	3	12 (20%)
(+)	(–)	4	1	0	2	5	12 (20%)
(+)	(+)	6	3	2	5	1	17 (28%)

TAE, ADM (10–20 mg) or FARM (30–60 mg) + Gelfoam + lipiodol; PEIT, percutaneous ethanol injection therapy; AI, hepatic arterial injection of ADM (10–20 mg) or FARM (30–60 mg) in the presence or absence of lipiodol using an injection capsule every 1 or 2 weeks

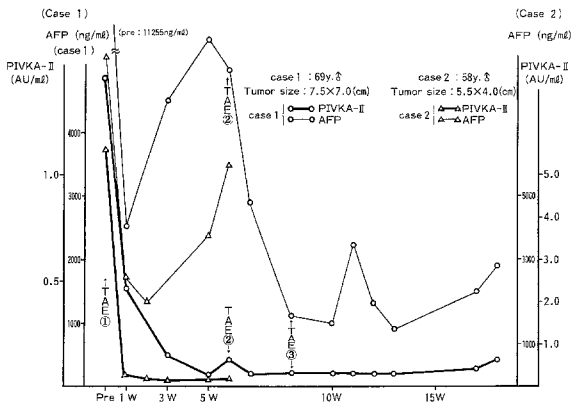

Fig. 2. Changes in PIVKA-II and AFP levels after TAE. *W*, week(s)

Table 4. Changes in PIVKA-II and AFP levels after treatment

	TAE	PEIT	PEIT +TAE	IA	Resection	Total
Before treatment:						
Number of patients.	25	12	4	7	13	61
PIVKA-II, ≥0.1 AU/ml	10	4	2	7	6	29 (47%)
After treatment:						
PIVKA-II ↓	7	3	2	2	5	19 (65%)
AFP, ≥200 ng/ml						
A↓,P↓	3	2	0	0	1	6
A→,P↓	3	0	1	0	0	4
A↓,P→	0	0	0	0	0	0
A↑,P↑	0	1	0	3	1	5

Changes in PIVKA-II and AFP levels after treatment

Of the 25 patients treated by TAE using ADM or FARM with lipiodol and Gelfoam, 10 were positive for PIVKA-II, and 6 of these 10 subjects were also positive for AFP. Corresponding changes in both tumor markers were detected in 5 patients (Fig. 2, case 1) after treatment. After hepatic arterial injection therapy, a gradual decrease in PIVKA-II levels was seen in 4 subjects, but in the remaining 3 patients, no meaningful change was recognized due to large fluctuations in PIVKA-II levels after treatment. Of the 13 patients who underwent hepatic resection, 7 demonstrated PIVKA-II levels of <0.1 AU/ml. In 5 of the remaining 6 patients, PIVKA-II values fell to levels within the normal range immediately after tumor resection (Table 4).

One of the patients who was negative for PIVKA-II before undergoing tumor resection showed an elevation in this marker at 21 months after surgery. Tumor recurrence was detected by imaging studies of CT and echography. It was noteworthy that a discrepancy in the changes in PIVKA-II and AFP levels was detected in 3/17 patients who had tested positive for both tumor markers (Fig. 2, case 2).

Discussion

In Japan, several therapeutic modalities are employed for the treatment of HCC, including transcatheter embolization (TAE), percutaneous ethanol injection therapy, and surgical resection. Evaluation of the efficacy of these treatments is often difficult due to the diverse clinical features of the patients. One of the more reliable approaches is to assess the changes in tumor markers after treatment, and we have used the serum AFP level as an indicator for the diagnosis of HCC and for monitoring of patients after treatment. However, the positivity rate for AFP in HCC is only around 50%.

Since Liebman et al. [3] first reported the usefulness of PIVKA-II as a tumor marker for HCC, several clinical studies have confirmed the high sensitivity of this marker [1, 2, 4]. In the current study, the overall positivity rate for PIVKA-II (>0.1 AU/ml) was 47%, whereas it ranged from 52% to 63.3% in other clinical investigations. Of our 61 patients, 30 (49%) showed elevated AFP levels (>200 ng/ml). We found no substantial correlation between the PIVKA-II values and the AFP levels, and 41/61 patients had elevated levels of one or both markers. Accordingly, the HCC detection rate was increased by about

Table 3. Relationship of PIVKA-II and AFP levels to cirrhosis, HBsAg positivity, and tumor size

		LC		HBsAg		Tumor Size (cm)			
		(–)	(+)	(–)	(+)	~2.0	2.1~5.0	5.1~10.0	10.1~
Number of patients		9	49	27	31	8	25	13	14
PIVKA-II (AU/ml)									
< 0.1		6	26	13	18	8	14	5	5
≧0.1		3	23	14	13	0	11	8	9
AFP (ng/ml)									
< 200		4	25	18	12	5	13	6	7
≧200		5	24	9	19	3	12	7	7
PIVKA-II	AFP								
(–)	(–)	3	17	11	8	5	8	4	3
(–)	(+)	3	9	2	10	3	6	1	2
(+)	(–)	1	8	7	4	0	5	2	4
(+)	(+)	2	15	7	9	0	6	6	5

20% by the measurement of both markers as compared with one parameter. However, none of the eight small HCCs measuring <2 cm in diameter showed a PIVKA-II level of greater than 0.1 AU/ml, whereas three of them were positive for AFP. This indicates that PIVKA-II may be less effective than AFP as a tumor marker for the early detection of HCC.

Measurement of plasma PIVKA-II levels seemed to be useful for the monitoring of HCC patients after treatment. In all, 29 of the 61 patients (47%) who received surgical or nonsurgical treatment had PIVKA-II levels of more than 0.1 AU/ml. Of the 6 surgically treated patients whose preoperative PIVKA-II values were high, 5 showed a fall in PIVKA-II levels to the normal range immediately after surgery, whereas only 2/7 patients receiving intra-arterial chemotherapy showed a reduction in PIVKA-II values during treatment. Of the 10 patients who tested positive for both PIVKA-II and AFP preoperatively, 6 showed a parallel decrease in the two markers after treatment, whereas a lack of agreement between these markers was observed in the other 4. At present, we do not have enough data to explain the discrepancy noted between these markers, but two possibilities can be suggested. The first would be that a mild elevation in AFP levels might have been produced by the noncancerous cirrhotic region. The second possibility would be that the administration of vitamin K after treatment may have affected PIVKA-II levels. Although there are some clinical and serological problems as mentioned above, we confirmed the usefulness of the plasma PIVKA-II level as a tumor marker in the diagnosis of HCC as well as in the monitoring of patients after treatment.

References

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