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New development of transarterial immunoembolization (TIE) for therapy of hepatocellular carcinoma with intrahepatic metastases

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Abstract. The prognosis of patients with multiple hepatocellular carcinoma (HCC) remains disappointing. In this study, we devised a new therapeutic modality for HCC consisting of transarterial immunoembolization (TIE) using OK-432 and fibrinogen and then analyzed the preliminary results. In the first series, we applied the treatment to 19 patients with advanced HCC who had proved to be insensitive to several previous conventional treatments. In all, 14 patients (74%) with unresected HCC have currently survived for between 2 and 16 months after TIE. The remaining 5 patients died at 17, 14, 8, 7, and 4 months after TIE. The serum levels of tumor markers decreased in all of the patients, and a marked reduction in tumor size was observed in six patients after TIE. A high fever occurred in all cases, and abdominal pain and loss of appetite were also observed after TIE. However, deterioration of liver function was negligible. After confirmation of the safety of this method, we started a second study series in which this TIE treatment was selected as the first choice. Six patients have been treated to date. All patients in this group underwent hepatic resection at 6–48 days following TIE. Histological examination of the resected specimens following TIE showed massive infiltration of mononuclear cells around tumor cell nests and lytic necrosis as well as coagulation necrosis of the main tumor and the intrahepatic metastases. In conclusion, our results indicate that TIE may be a safe and promising therapy for patients with HCC.

Introduction

At present, surgical resection [6, 21], transcatheter arterial embolization (TAE) [15, 24, 28] and percutaneous ethanol injection therapy (PEIT) [9, 19, 20] are considered to be the most effective treatments among the many therapeutic modalities devised to date for hepatocellular carcinoma (HCC). However, the prognosis of patients with multiple HCC remains disappointing even following their treatment by these methods. We previously reported a 69.1% 5-year survival rate for cases without intrahepatic metastases after resection as compared with 22% for cases with intrahepatic metastases in one segment of the liver [10]. It thus remains necessary to develop a more effective treatment for HCC with intrahepatic metastases. Therefore, we devised a new therapy consisting of transarterial immunoembolization (TIE) using OK-432 and fibrinogen, which has been reported to enhance not only the systemic immunological potential but also the local cytotoxicity against colorectal cancer [11].

In the present study, we analyzed our preliminary results for the clinical efficacy and safety of TIE in HCC cases. The efficacy and side effects of TIE were examined in inoperable patients with advanced HCC who had not responded to conventional treatments such as TAE and PEIT. We also analyzed the histological findings obtained in resected tumor specimens from six patients who had undergone TIE as initial therapy.

Patients and methods

Patients. TIE therapy was performed a total of 28 times on 25 patients with HCC at Osaka University Hospital between September 1991 and March 1993. All patients who had undergone hepatic resection were histologically confirmed as having HCC, whereas those with progressive or multiple liver cancer who had not undergone surgery were diagnosed as having HCC on the basis of radiological and biochemical findings. In all, 19 of those patients were inoperable cases of advanced HCC that were treated with TIE in the first series. After confirmation of the safety of this method, we started a second study series in which this TIE treatment was selected as the first choice. Six patients have

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Table 1. Clinical characteristics of patients

		TIE	TIE + Resection
No. of patients		19	6
Sex:			
	M	16	4
	F	3	2
Age (years):			
	40–49	4	0
	50–59	3	3
	60–69	9	1
	>70	3	2
No. of tumors:			
	Single	1	6
	Multiple	18	0
AFP (ng/ml):			
	<100	9	3
	100–999	5	3
	>1000	5	0
PIVKA-II (AU/ml):			
	<0.1	5	3
	>0.1	14	3
Total bilirubin (mg/dl):			
	<2.0	19	6
	2.0–3.0	0	0
	>3.0	0	0
Serum albumin (g/dl):			
	>3.5	10	6
	3.0–3.5	6	0
	<3.0	0	0
	Unknown	3	0
Prothrombin time (%):			
	>80	1	1
	50–80	16	5
	<50	0	0
	Unknown	2	0

been treated to date. All of the patients in this group underwent hepatic resection following TIE. The clinical characteristics of the patients are shown in Table 1.

Biological response modifier (BRM). OK-432 is a penicillin-treated lyophilized powder of the avirulent Su strain of group A *Streptococcus pyogenes* of human origin [13]. The Klinische Einheit unit (KE) is used to express the strength of the preparation; 1 KE of OK-432 is equivalent to 0.1 mg of dried streptococcal cells.

Fibrinogen. A commercially available fibrin glue that contains Factor-XIII was chosen for use in this study.

TIE procedure. TIE therapy was performed according to our protocol. Briefly, a vascular catheter was inserted into the tumor-feeding artery, such as the proper hepatic artery or its branches. A double catheter, i.e., a balloon catheter and an S-P catheter, was utilized as shown in Fig. 1. OK-432 (2.5 KE/ml), fibrinogen (60 mg/ml), and thrombin (1 U/ml) were individually dissolved in saline and then mixed together. Under this condition, conversion of the fibrinogen into stable fibrin occurred at 2.5 min after mixing at room temperature. Next, Lipiodol was added to the mixture at a ratio of 1:4. Approximately 5–10 ml of the mixture was injected through the S-P catheter after the hepatic artery flow had been decreased by blowing up the balloon catheter. All of these procedures were completed within 2 minutes of the preparation of the fibrinogen and thrombin mixture. No anticancer drug was used.

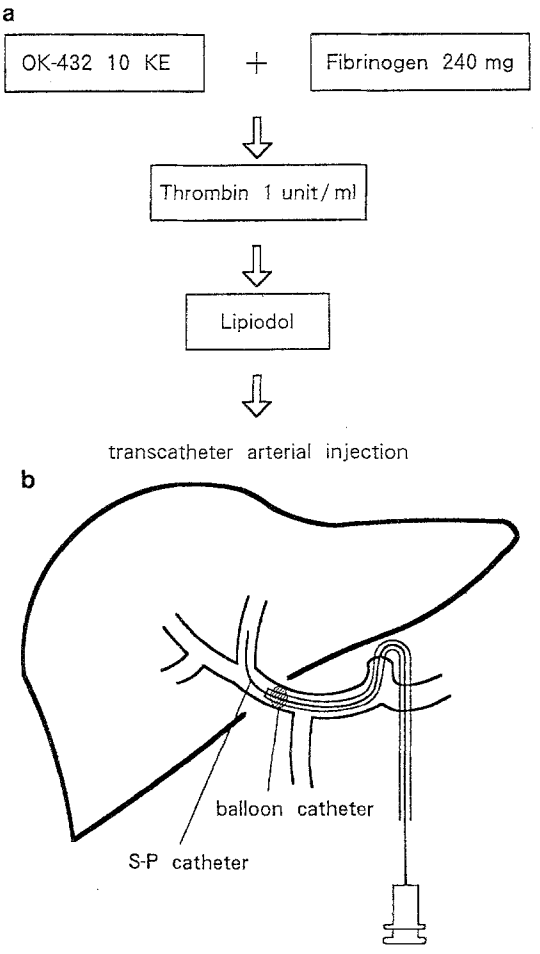

Fig. 1. Schema of the TIE procedure. OK-432 (2.5 KE/ml), fibrinogen (60 mg/ml), and thrombin (1 U/ml) were individually dissolved in saline and then mixed together. Lipiodol was also added to the mixture at a ratio of 1:4 (**a**). Approximately 5–10 ml was injected through the S-P catheter after the blood flow had been decreased by the balloon catheter (**b**)

Assessment. The liver function tests, the serum level of tumor markers [alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (PIVKA-II)], and the size of the tumor were serially examined to assess the clinical responses and side effects of this therapy. The response was determined on the basis of computerized tomography (CT) scan or ultrasound findings. Histological examination was performed to assess the pathological response using tumor specimens resected after TIE.

Results

The efficacy and side effects of TIE were investigated in 19 inoperable patients with multiple HCC. The results are summarized in Table 2. The follow-up period ranged from 2 to 17 months. Four patients died of the carcinoma at 17, 16, 8, and 4 months after the TIE. One patient died of heart failure unrelated to the TIE. The remaining 14 patients (74%) are currently alive, with 4 patients having survived for 14, 14, 16, and 16 months, respectively. In all patients with a high AFP level of more than 100 ng/ml or a PIVKA-II value of more than 0.1 AU/ml, the serum AFP or PIVKA-II level decreased promptly after the TIE. Fur-

Table 2. The results of TIE in inoperable patients

Case	Age (yr)	Sex	Location of tumor	Initial treatment	Date of TIE	Initial AFP (ng/ml)	Outcome
1 MT	60	M		subsegmentectomy (S_6) TAE (3)	1991. 9. 10 1991. 9. 17	20193	Dead (17 M)
2 SO	50	M		TAE (3)	1991. 11. 8	98	Alive (16 M)
3 AI	62	M		lateral segmentectomy TAE (1)	1991. 11. 22	12279	Alive (16 M)
4 TY	46	M		posterior segmentectomy LAK·TAE (1)	1992. 1. 8 1992. 4. 24	11	Alive (14 M)
5 IT	59	M		subsegmentectomy (S_6) TAE (2)	1992. 1. 29	2250	Dead (14 M)
6 KS	67	M		TAE (2)	1992. 2. 4	10	Alive (14 M)
7 ND	71	M		TAE (2)	1992. 4. 23	428	Alive (11 M)
8 MI	67	M		TAE (3)	1992. 7. 17	45	Alive (8 M)
9 YK	51	M		subsegmentectomy (S_6) TAE (1)	1992. 7. 31 1993. 1. 29	2326	Dead (8 M)
10 YK	74	M			1992. 8. 26	392	Dead (7 M)
11 MO	44	M		TAE (1)	1992. 9. 4	174	Alive (7 M)
12 NY	54	M		partial resection (S_3) TAE (1)	1992. 9. 11	282	Alive (7 M)
13 MI	60	M		TAE (2)	1992. 9. 16	32	Alive (7 M)
14 TY	66	F		TAE (4)	1992. 10. 30	3093	Alive (5 M)
15 YU	57	M		TAE (1)	1992. 11. 6	12	Dead (4 M)
16 YT	66	M			1992. 11. 11	11	Alive (4 M)
17 SF	61	F		TAE (2)	1992. 12. 18	2580	Alive (3 M)
18 MN	77	F		TAE (2)	1993. 1. 12	91	Alive (3 M)
19 YY	38	M		TAE (1) PEIT (1)	1993. 1. 27	236	Alive (2 M)

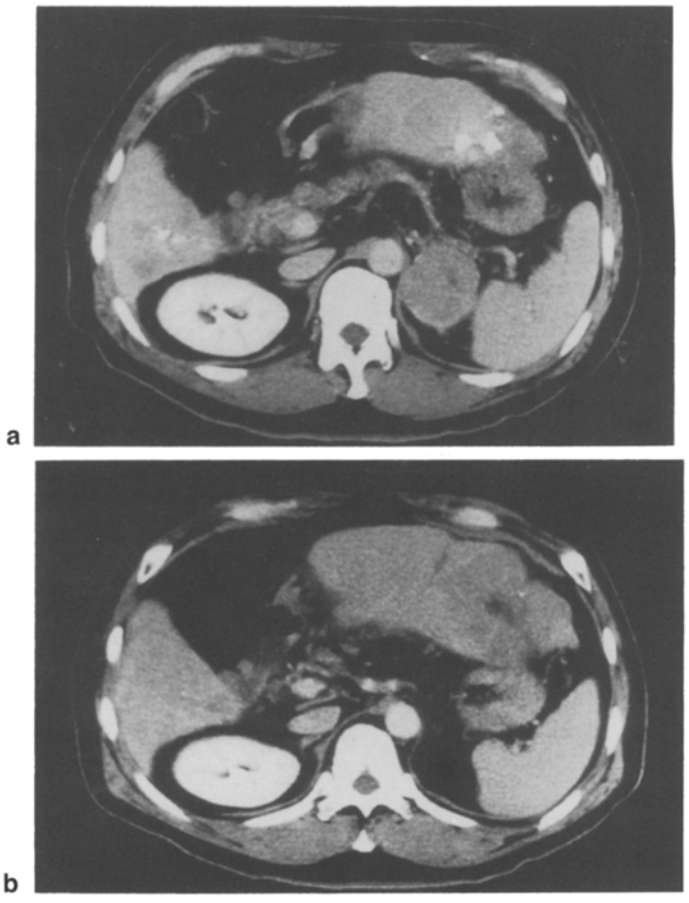

Fig. 2. Abdominal CT scan findings of an unresectable patient with multiple HCC before and after TIE therapy. **a** Before TIE therapy. **b** At 3 months after TIE therapy. The tumors in S2 and S8 have become lower in density and decreased markedly in size after TIE therapy

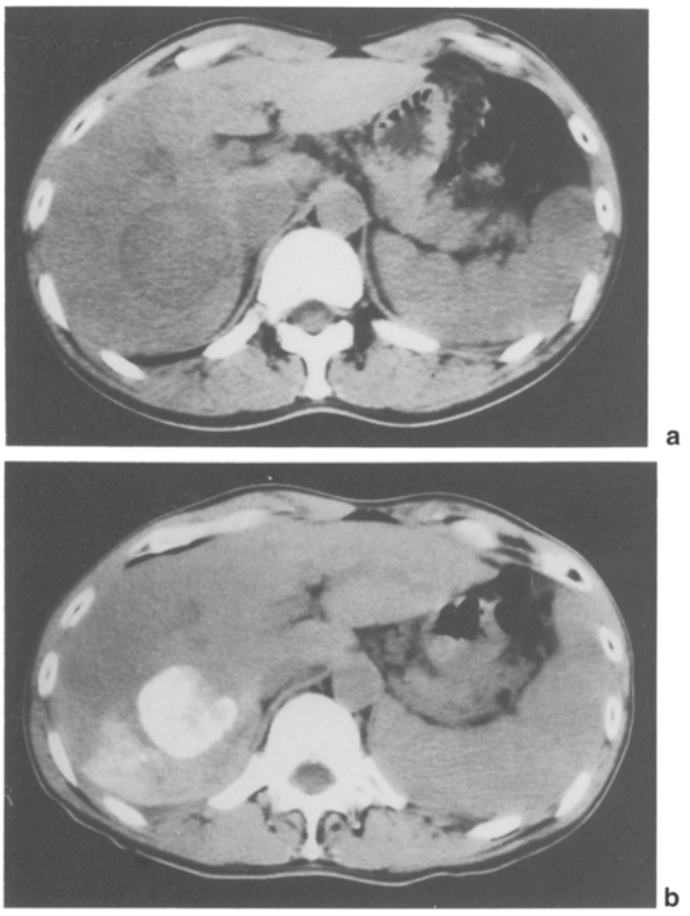

Fig. 3. Abdominal CT-scan findings of a resectable patient with HCC before and after TIE therapy. **a** A CT scan showing a low-density area in the right hepatic lobe before TIE. **b** A CT scan showing that the space-occupying lesion has changed to a high-density area due to Lipiodol accumulation on day 5 after TIE

Table 3. Incidence of side effects after TIE

Side effects	No. of patients (%)
Symptom:	
Fever	18/18 (100%)
Abdominal pain	7/18 (39%)
Loss of appetite	6/18 (33%)
Nausea	2/18 (11%)
Vomiting	2/18 (11%)
Laboratory data:	
GOT (>400 U/l)	3/13 (23%)
T. Bil. (>2.0 mg/dl)	3/13 (23%)
BUN (>30 mg/dl)	2/14 (14%)
WBC (/μl)	
10,000–20,000	10/15 (67%)
>20,000	2/15 (13%)
Platelets (/μl)	
<50,000	5/15 (33%)

thermore, a marked reduction in tumor size was observed in six patients after the TIE. Figure 2 shows an abdominal CT scan of a 60-year-old man who was the first to be treated with TIE. A remarkable reduction in the tumor size was observed at 3 months after TIE.

Table 3 presents the data on the incidence of side effects after TIE. A high fever occurred in all of the cases; abdominal pain, in 7/18 (39%) cases; and loss of appetite in 6/18 (33%) cases. The white cell count in peripheral blood increased to over 20,000/μl after TIE in 2 cases, and the serum GOT level increased to more than 400 U/l in 3 of 13 cases. However, in all of the cases it decreased to the pretreatment level within 1 week of TIE. Coagulation parameters such as the prothrombin time, hepaplastin test, and fibrinogen/fibrin degradation products (FDP) were also serially examined. No disturbance of the coagulation-fibrinolysis system due to TIE was observed in any of the patients. These findings indicate that TIE has a negligible negative influence on the liver function. Again, the major side effect of this therapy was a high fever of more than 38° C, which generally manifested immediately after this procedure. This was probably related to the OK-432, since this kind of fever is not usually observed after conventional TAE. However, in all of the patients, the transarterial injection of OK-432 and fibrinogen was well tolerated.

Since it was concluded that the adverse effects of TIE could be considered negligible as compared with those of TAE, we started a second study series. We performed TIE in six patients with operable HCC to assess the efficacy of TIE histologically. Hepatic resection was performed in six patients at 6, 6, 11, 20, 23, and 48 days following TIE.

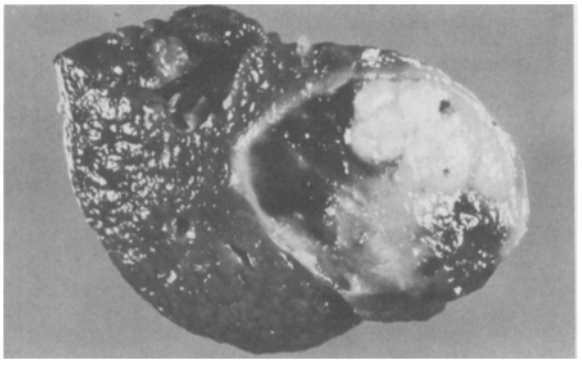

Fig. 4. Resected specimen. S7 subsegmentectomy was performed on day 11 after TIE. The gross findings show that the tumor is well encapsulated and contains hemorrhagic lesions

Histological examination showed a massive infiltration of mononuclear cells around the tumor cell nests in all of the patients. Lytic necrosis as well as coagulation necrosis of the main tumor was observed in four of the six cases, and lytic necrosis of the intrahepatic metastases was observed in two of three cases with intrahepatic metastases. These findings were different from those observed following conventional TAE.

Figure 3 shows an abdominal CT scan of a 50-year-old man with HCC who underwent hepatic resection on day 11 following TIE. A CT scan revealed a low-density area in the right hepatic lobe, and the area had changed to a high-density area due to Lipiodol accumulation at 5 days after TIE. The gross findings for the resected mass showed that the tumor was well encapsulated and contained hemorrhagic lesions (Fig. 4). Microscopic inspection showed that a massive infiltration of mononuclear cells was focused on destroyed tumor cell nests. Also, fibrin clots were observed in the vessels of the tumor, which was surrounded by a severe infiltration of lymphocytes (Fig. 5). Interestingly, similar findings were observed in the intrahepatic metastases (Fig. 6). In summary, we found that TIE using OK-432 and fibrinogen enhanced not only the systemic immunological potential but also the local cytotoxicity toward HCC.

Discussion

The outcome of patients with HCC has generally been considered to be very poor. To date, remarkable progress in imaging modalities has made it possible to diagnose small HCC [3]. Improvements in liver surgery, including precise

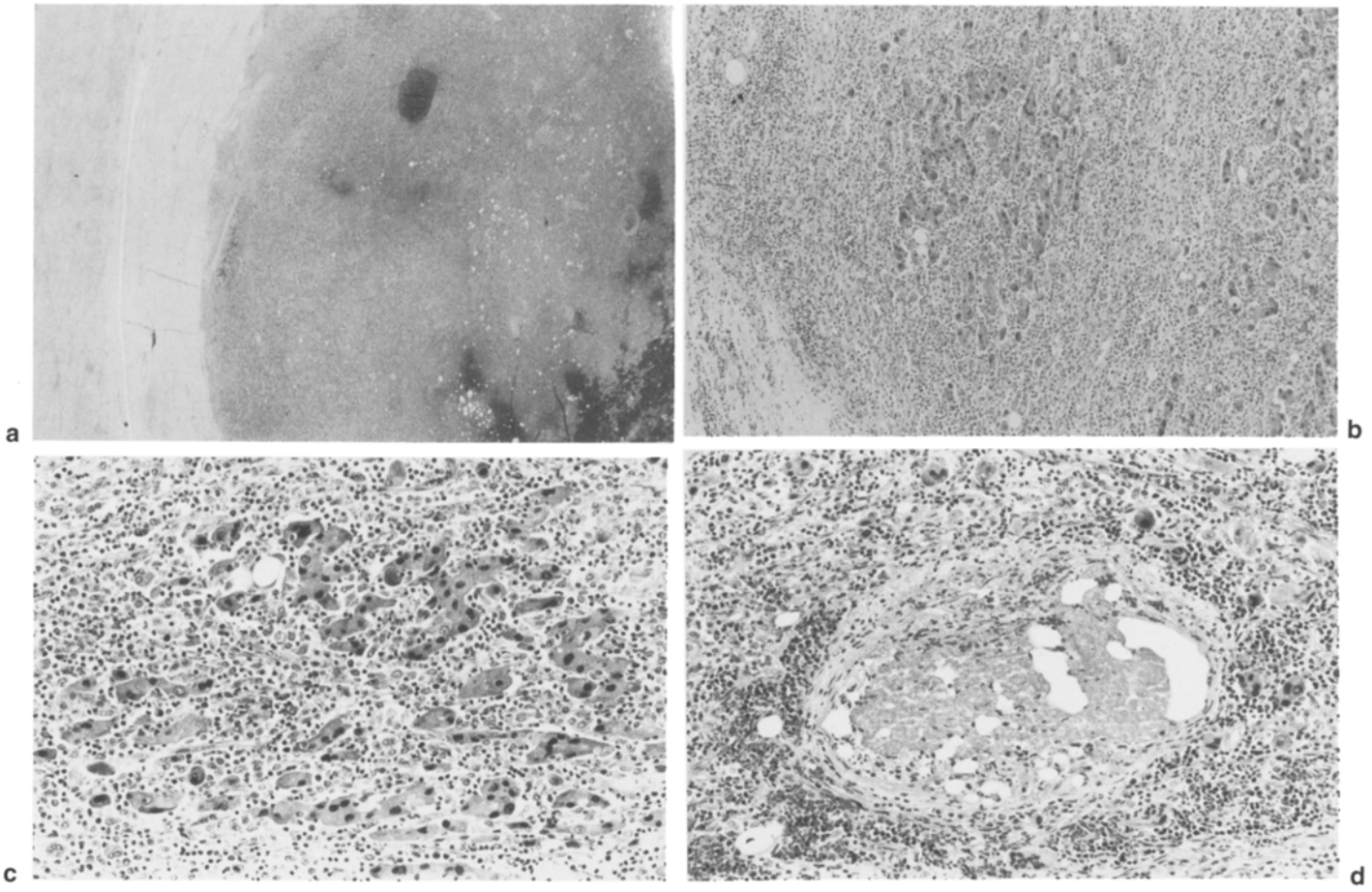

Fig. 5. Microscopic findings of the main tumor. **a** Coagulation necrosis and lytic necrosis of the main tumor (H & E, ×7.5). **b** Lytic necrosis of the main tumor (H & E, ×75). **c** Massive infiltration of mononuclear cells around destroyed tumor cell nests (H & E, ×150). **d** Fibrin clots in the vessels of the tumor (H & E, ×150)

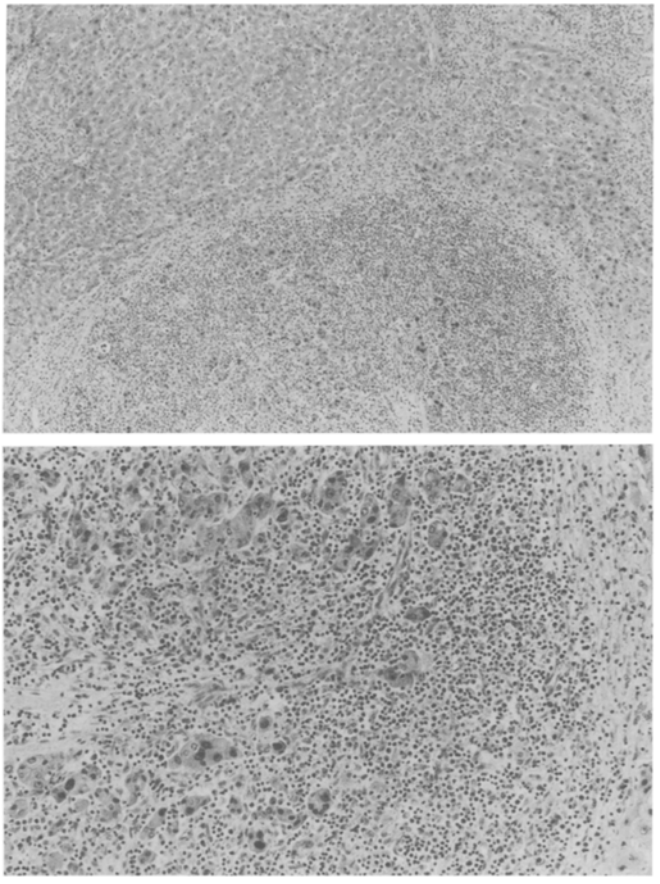

Fig. 6. Microscopic findings of the intrahepatic metastasis. **a** Lytic necrosis of the intrahepatic metastasis (H & E, ×45). **b** Massive infiltration of mononuclear cells around destroyed tumor cell nests (H & E, ×100)

assessment of the liver function, new surgical approaches using intraoperative ultrasonography, and fine postoperative management, have led to a great increase in the resectability rate, a decrease in operative mortality, and a better survival rate after resection [14]. It has been shown that long-term survivors are limited to those who have undergone complete surgical resection of the tumor. According to the report by the Liver Cancer Study Group of Japan, the overall 5-year survival of HCC patients is 35.2% after surgical resection [8]. However, the long-term survival of patients with multiple HCC remains unsatisfactory.

TAE is indeed an excellent radiological procedure for achieving significant palliation in patients with unresectable HCC [12, 15, 28]. Histopathology studies have demonstrated that TAE is quite effective for the main tumors but not very effective for small intrahepatic metastases, which are reported to be the key lesions in determining the prognosis [18, 24]. The difference in effectiveness is attributable to differences in the blood supply. Small intrahepatic metastases are presumed to receive a dual supply of blood, i.e., through the portal vein as well as the hepatic artery, whereas larger tumors are dependent only on the arterial blood supply [2]. Much of the cytotoxic effect of TAE derives from its complete obstruction of the blood supply to tumors. It is conceivable that small metastatic lesions are not as sensitive to TAE treatment because the blood supply is not adequately obstructed.

In the present study, we devised a new therapeutic modality, namely, transarterial immunoembolization (TIE) using OK-432 and fibrinogen, for the treatment of HCC. The OK-432 was given with fibrinogen, thrombin, and Lipiodol using our own technique as described in Patients and methods.

The TIE treatment induced a decrease in the serum AFP level of PIVKA-II level and a marked reduction in the tumor size as detected on abdominal CT scans both in patients who had undergone previous treatments and in those who were treated for the first time. Our histological examinations also revealed necrotic changes not only in the main tumor but also in the small intrahepatic metastases, which have been reported to be difficult to treat with TAE and other methods.

The tumors treated by this TIE method showed two types of tumor necrosis: coagulation necrosis and lytic necrosis. The former is commonly seen in patients treated by conventional TAE, whereas the latter is not observed. As shown in Figs. 3–5, tumors undergoing lytic necrosis have an arterial blood supply and also viable mononuclear cells surrounding the tumor cells. This phenomenon is a completely different finding as compared with that following TAE, and it might be responsible for the effectiveness of TIE on small metastatic lesions. Whatever the mechanism is, TIE is probably more effective than TAE, especially against HCC with intrahepatic metastases.

OK-432 has been extensively used as a biological response modifier (BRM) in Japan. Peripheral blood mononuclear cells in normal subjects treated with OK-432 have been shown to express cytotoxic activity against various tumor cell lines. In humans, OK-432 has been reported to improve the survival and response rates of patients with some forms of cancer [5, 22, 23, 26]. In experimental studies, OK-432 has been shown to augment cytotoxic macrophages [7], natural killer (NK) cell activity [1, 25], and lymphokine-activated killer cell activity [17], and OK-432 also induces the production of various cytokines such as interferon (IFN) [16], tumor necrosis factor (TNF), interleukin 1, interleukin 2, and interleukin 6 [4]. Thus, OK-432 is a varied biological, immunological potentiator and cancer chemotherapeutic agent.

A single injection of OK-432 mixed with fibrinogen into mouse subcutaneous tissues caused prolonged accumulation of OK-432 and induced a marked infiltration of inflammatory cells as compared with OK-432 alone [27]. The antitumor effect of OK-432 on colorectal carcinoma was greatly augmented when it was injected intratumorally together with fibrinogen. This immunotherapy seemed to enhance efficiently the antitumor effect of OK-432 by altering the fibrin metabolism in the cancer stroma [11]. In addition, fibrinogen can be easily delivered into tumor vessels and is distributed more diffusely throughout the liver than are gelatin particles. Thrombin converts fibrinogen into a network of stable fibrin strands. During fibrin formation, OK-432 binds to the fibrin. On the other hand, since tissue plasminogen activator released from the vessel wall enhances the proteolytic cleavage of plasminogen to plasmin, OK-432 encapsulated in an insoluble

fibrin clot may be gradually released from this clot into the tumor tissue. The exact mechanism in regard to the functions of fibrin and fibrinogen in this therapy remains unclear. The significance of fibrin and fibrinogen is worthy of future investigation.

Furthermore, Lipiodol, a lipid lymphographic agent, injected into the hepatic artery, remained selectively in the hepatic tumor tissue for a long period. The method using Lipiodol increases the necrotic effect on intrahepatic metastases [12]. Even if the feeding artery were embolized by fibrin and Lipiodol, OK-432 would nonetheless be acting on the tumor tissue through the portal vein. Therefore, the lesion could be completely treated by TIE.

Our patients often complained of fever, nausea, and abdominal pain after the TIE. In particular, a high fever of more than 38°C is thought to have been caused by the OK-432. However, this TIE therapy did not cause any serious side effects. Our results clearly showed that this TIE therapy was quite safe and beneficial in the treatment of advanced HCC, although this study was not a randomized, controlled clinical trial. As our cases included many advanced cases, even better clinical responses might be achieved in patients in better health. Further investigation is required for a final evaluation of the usefulness of TIE.

In conclusion, our results suggest that TIE is a safe and effective therapy for HCC patients with intrahepatic metastases and achieves a considerable improvement in the prognosis of patients with multiple HCC. We believe that TIE is a promising modality for the treatment of HCC with intrahepatic metastases.

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