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Combination therapy of transcatheter chemoembolization and percutaneous ethanol injection therapy for unresectable hepatocellular carcinoma

Toshiyuki Kato, Yukifumi Saito, Masayuki Niwa, Jun Ishiguro, Kazuei Ogoshi

Division of Internal Medicine, Niigata Cancer Center Hospital, Niigata 951, Japan

Abstract. The therapeutic effectiveness of a combination therapy – pretreatment with transcatheter arterial chemoembolization (TACE) followed by percutaneous ethanol injection (PEI) therapy – for large (>3 cm in diameter) unresectable hepatocellular carcinoma (HCC) was compared with that of TACE alone. PEI therapy was performed in 24 cases of unresectable HCC that had previously been treated with TACE using doxorubicin 30–60 mg or epirubicin 50–90 mg. In all, 2–10 ml of 90% ethanol mixed with carbocaine was repeatedly injected through a 21-gauge, closed-end needle (PEIT needle) for a median of 3.6 injections and 31.1 ml of ethanol. As adverse effects, transient localized pain and a burning sensation were observed in 75.0% of the cases; fever, in 66.7%; and transient hypotension, in two cases. A small unresectable tumor is a good indication for PEI therapy. In cases with a larger tumor, i.e., measuring more than 3 cm in diameter, or multiple tumors, the 1-year survival rate obtained with this combination therapy, i.e., TACE and PEI, was 87.0%, and the 2-year survival rate was 65.2%. These rates were greater than those obtained with TACE alone. Accordingly, additional PEI therapy was effective for larger tumors and multiple tumors previously treated with TACE.

Introduction

Hepatocellular carcinoma (HCC) has been considered to be a highly malignant tumor with a poor prognosis [4, 13]. In patients with HCC that is unresectable because of its advanced stage or poor surgical risk due to severe liver dysfunction, transcatheter embolization (TAE) or chemotherapy has been performed [14]. Recently, ultrasonically guided percutaneous ethanol injection (PEI) therapy has been developed for the treatment of HCC [2, 5, 8–10]. Because PEI therapy is effective for small HCC, a small unresectable tumor measuring less than 3 cm in diameter is considered to be a good indication for PEI therapy [5].

Larger tumors measuring more than 3 cm in diameter require additional therapy after TAE or transcatheter arterial chemoembolization (TACE) [11, 12]. The present study evaluated a combination therapy consisting of TACE and PEI therapy.

Patients and methods

Patients. Between December 1986 and December 1992, 46 patients with large, encapsulated HCC lesions were treated at the Division of Internal Medicine, Niigata Cancer Center Hospital. In all, 28 of the patients were men and 18 were women; their age ranged from 44 to 78 years (mean, 64.2 years). The criteria for entry into this study were (a) the liver tumor lesions were three or fewer in number and larger than 3 cm in diameter (maximum, 12 cm), (b) the lesions were detectable by US, and (c) the patiens had no portal thrombosis, extrahepatic metastasis, or ascites. In all, 32 of the patients had cirrhosis of the liver. The diagnosis of HCC was made by means of pathologic examination of biopsy (n = 22) or autopsy (n = 24) specimens in all patients. Surgical resection had not been performed in any of these patients because of the advanced stage of the disease (n = 24), advanced liver failure (n = 12), old age (n = 8), or the presence of new lesions in a previously resected liver (n = 2).

Patients eligible for the study were alternately assigned to one of two groups (TACE alone or TACE combined with PEI). PEI therapy was performed in 24 cases of unresectable HCC that had previously undergone TACE using doxorubicin or epirubicin. In the remaining 22 cases, TACE was performed alone because anatomic variations or ascites precluded PEI. The patients in the two groups did not differ significantly in terms of the various background factors analyzed (Table 1).

Methods. The equipment used for PEI consisted of a commercially available US scanner equipped with 3.5-MHz real-time convex probes and a lateral attachable apparatus for needle guidance (SSD 750; Aloka, Tokyo). Sterile ethyl alcohol (90%–95%) mixed with carbocaine was injected using a PEIT needle (Nagano Hakko; Nagano), which was a 21-gauge spinal needle with three side holes [1]. Alcohol was injected slowly in a volume of 2–10 ml/session in proportion to

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Correspondence to: T. Kato, Division of Internal Medicine, Niigata Cancer Center Hospital, 2-15, Kawagishi-cho, Niigata 951, Japan

Table 1. Background factors of the patients

Factor		TACE alone	TACE+ PEI	
No. of patients		22	24	
Age (years)	Mean	64.5	61.3	NS
	Range	44–78	44–78	
Sex (M/F)		13/9	15/9	NS
HBsAg-positive (%)		7 (31.8)	3 (12.5)	NS
Anti-HCVAb-positive (%)		14 (63.6)	17 (70.8)	NS
Pre-TACE AFP (ng/ml)	<20	4	7	
	20–99	7	4	NS
	100–999	2	5	
	≧1,000	9	8	
Largest tumor diameter (cm)	Median [25,75%]	7.09 [4.0, 8.3]	6.52 [3.8, 7.6]	NS
Liver cirrhosis	No	8	9	NS
	Yes (%)	14 (63.6)	15 (62.5)	
Child's class (A/B/C)		17/5/0	19/5/0	NS
TACE Doxorubicin (mg/body)		55.2 (30–60)	53.4 (30–60)	
or epirubicin		70.6 (45–90)	74.4 (45–90)	
PEI No. of injections (median)		0	3.6 (1–11)	
Total volume (ml, median)		0 [25,75%]	31.1 (2–112) [8,46]	

NS, not significant

the size of the lesion. During ultrasonographic monitoring of the procedure, the ethanol was continuously injected until the tumor was completely filled with ethanol and became highly echogenic (Fig. 1).

TACE was performed by selectively introducing a catheter into the hepatic artery and injecting a mixture of iodized oil (Lipiodol; range, 3–10 ml) and an anticancer drug, either doxorubicin (Adriamycin; 0.6–1.0 mg/kg; dose range, 30–60 mg) or epirubicin (Farmorubicin; 1.0–1.5 mg/kg; dose range, 45–90 mg), followed by gelatin sponge (Gelfoam; 1 × 1 × 1 mm).

Treatment protocol. At 1 week after TACE, PEI therapy was performed two or three times a week until the total ethanol dose reached the intended volume according to the lesion size and the patient's tolerance. The total volume of ethanol ranged from 2 to 109 ml (median, 31.1 ml). This PEI therapy was repeated up to 11 times for a median of 3.6 times (Table 1).

Assessment of the treatment results. After the TACE and PEI therapy, the responses to the therapy were evaluated on the basis of the US and CT findings, the serum level of α-fetoprotein (AFP), and the survival rates.

Results

Tumor response

Follow-up CT and US were performed to evaluate the effectiveness. After completion of the TACE and PEI combination therapy, a marked volume reduction (>50%) was observed in 9 (37.5%) of the 24 patients. Maximal reduction ranging from 0 to 72% of the initial volume was recorded.

Serial changes in AFP and liver function parameters

Of the 13 patients whose pretreatment AFP values exceeded 100 ng/ml, the level in 8 exceeded 1,000 ng/ml.

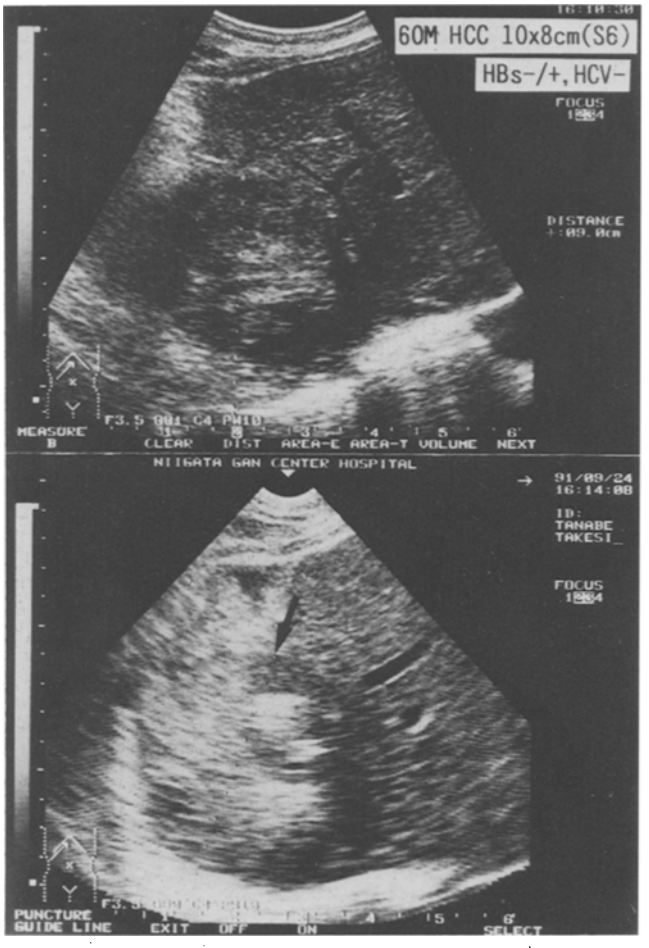

Fig. 1. US images of a patient, obtained before and after PEI. (**a**) Before PEI, the lesion had mixed echogenicity (**b**) During ultrasonographic monitoring of the procedure, the lesion was completely filled with ethanol and became highly echogenic

After completion of the TAE and PEI combination therapy, the level of AFP decreased in all 13 patients. In 4 patients, the level of AFP was reduced to less than 20 ng/ml, and in 9 other patients it was reduced to between 20 and 1,000 ng/ml.

Survival

In the 22 patients with a larger HCC tumor measuring more than 3 cm in diameter or multiple tumors treated with TACE alone, the survival rates at 1, 2, and 3 years were 50.7%, 31.7%, and 8.5%, respectively. Of 24 patients with a larger tumor treated with combination TACE and PEI therapy, 5 were alive at the end of the study. The 1-, 2-, and 3-year survival rates were 87.0%, 65.2%, and 39.7%, respectively. The survival rates resulting from the combination therapy were better than those obtained with TACE alone (Fig. 2).

Side effects

After the injection of ethanol, transient localized pain and a burning sensation were experienced by 18 patients (75.0%),

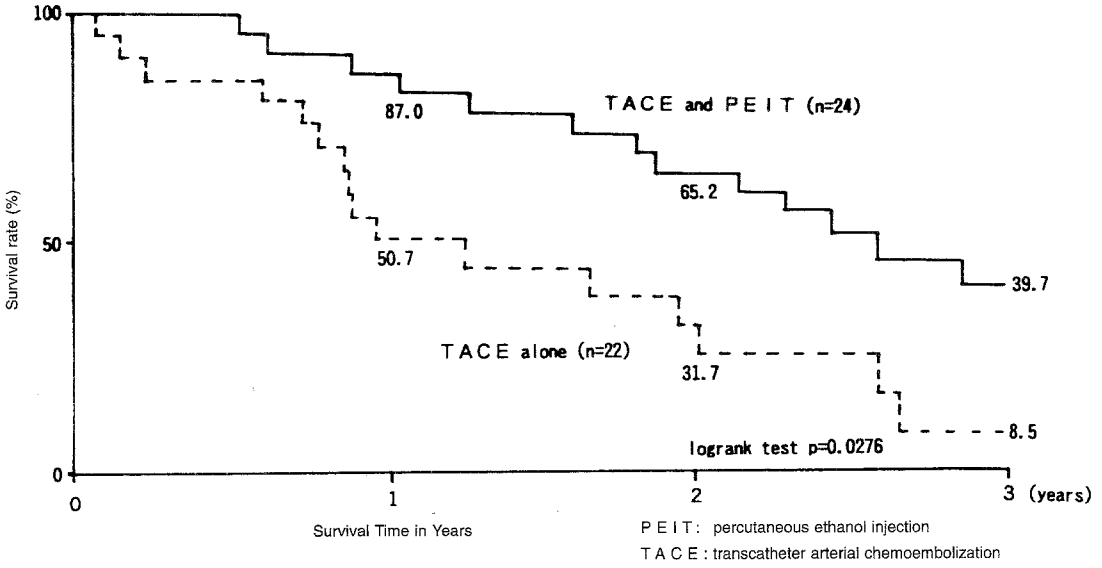

Fig. 2. Survival curves of patients with HCCs measuring more than 3 cm in diameter

Table 2. Complications after ethanol injection

Complication	No. of patients 24	No. of injections 88
Transient local pain	18 (75.0%)	52 (59.1%)
Mild fever	16 (66.7%)	46 (52.3%)
Intraperitoneal hemorrhage	0	0
Local dissemination	0	0
Transient hypotension	2 (8.3%)	2 (2.3%)
Hepatic infarction	0	0
Hemobilia	0	0

with 52 such events (59.1%) being reported (Table 2). Mild fever occurred in 16 patients (66.7%) on 46 occasions (52.3%). Transient hypotension, which recovered with conservative treatment, was detected in 2 patients due to leakage of ethanol into the peritoneal cavity. No death occurred that was directly related to the PEI or TACE treatment.

Representative case

A 60-year-old man was admitted with pain in the right hypochondrium. The serum AFP level was 138,600 ng/ml. Abdominal US examination revealed a huge mass (10 × 9 × 8 cm) with several nodules in the right lobe. Needle-aspiration biopsy of the mass confirmed it to be HCC (Edmondson's grade II). TACE using epirubicin (Farmorubicin) at 90 mg/body was performed. After 2 weeks, ethanol (PEI) was repeatedly injected three times to a total volume of 34 ml (Fig. 1). After completion of the combination TACE and PEI protocol, the follow-up CT scan showed a partial response (PR), since the diameter of the mass had decreased to 6 cm (Fig. 3). The serum AFP level had decreased to 220 ng/ml (0.2%). This patient has survived for 22 months since the treatment.

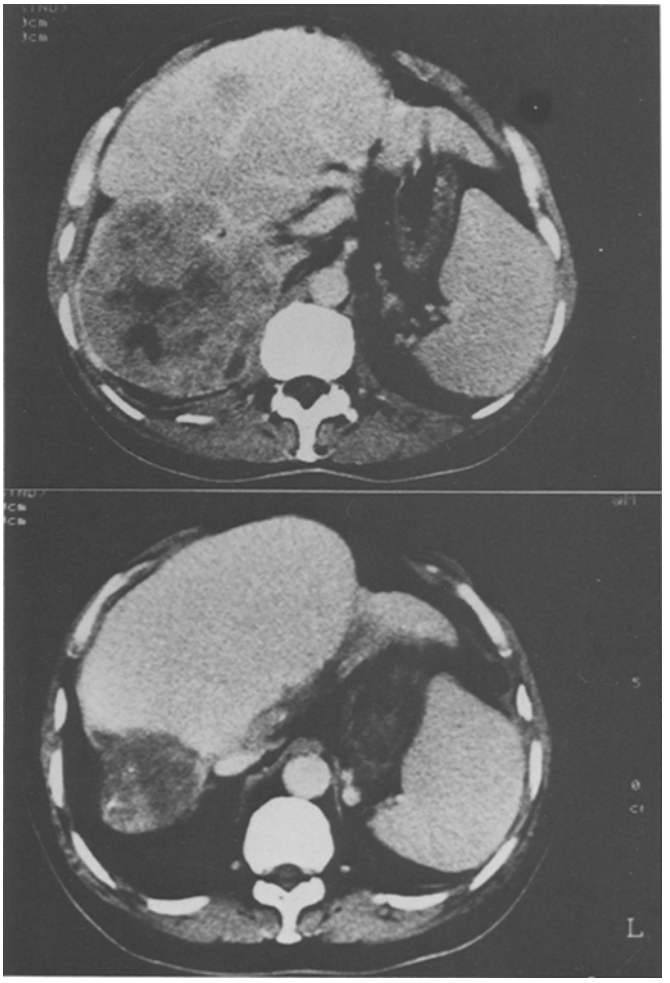

Fig. 3. A 60-year-old man underwent PEI therapy following TACE. (**a**) This CT scan shows a large tumor in the right lobe of the liver (August 19, 1991) (**b**) About 16 months after TACE and PEI, this CT scan shows a marked reduction in the tumor size (January 20, 1993). The patient achieved a PR and has survived for 22 months

Discussion

TAE therapy is very effective in the treatment of HCC [3, 14]. Recently, TACE has been shown to result in a survival rate better than that obtained with TAE alone [6, 7]. However, for a large lesion of HCC, since TAE or TACE alone often fail to bring about complete necrosis and the long-term survival rates are low, it is necessary to perform TAE or TACE repeatedly [7, 11].

PEI therapy is a safe, reproducible, easy-to-perform, and low-cost therapeutic technique. The alterations in liver function observed after PEI are much milder than the changes noted after TACE or surgical resection [9]. PEI can be considered for patients with severe liver dysfunction who cannot be treated by other procedures. PEI therapy has been performed as an effective treatment for small lesions of HCC [2, 5, 8–11]. Absolute ethanol destroys the cancer tissue immediately and directly, mainly through its dehydrative and protein-degenerative effects and partly through its thromboembolic effect. Livraghi et al. [5] showed that PEI resulted in complete necrosis of lesions smaller than 3.2 cm in diameter, and for 75 patients with lesions smaller than 3.0 cm in diameter, the 1-, 2-, and 3-year survival rates were 93%, 81%, and 65%, respectively. Shiina et al. [9] reported that the survival rates obtained in cases of small HCC did not differ between a PEI-alone group and a TACE-PEI group because the local effect of PEI was much greater than that of TACE.

The effectiveness of PEI has been limited to small HCC lesions [11]. Livraghi et al. [5] proposed that PEI should be considered to be the treatment of choice for single lesions smaller than 5 cm in diameter, which are considered to be inoperable. In lesions larger than 3 cm in diameter, it is difficult to inject ethanol throughout the entire tumor because of the texture of the tumor parenchyma. PEI is considered to be ineffective for large lesions due to the following reasons: (a) a large volume of ethanol must be injected, and (b) the high vascularity of HCC washes out the ethanol and reduces its toxic action [11].

To achieve more complete necrosis of large HCC lesions, we introduced the present combination therapy, PEI combined with TACE. Prior TAE makes the tumor parenchyma necrotic and enables the administration of a large volume of ethanol, filling the entire tumor with ethanol under high pressure and resulting in complete necrosis of even large lesions. After TAE, washout of the injected ethanol is more difficult in the tumorous area. Therefore, the ethanol can infiltrate the entire tumor, resulting in complete necrosis [11].

Additional PEI therapy was effective for larger tumors previously treated with TACE. Tanaka et al. [11] reported than the survival of 32 patients with large lesions (>3 cm in diameter) in a TAE-PEI group was significantly longer than that of patients in a TAE group. In the TAE-PEI group, the 1-, 2-, and 3-year survival rates were 100%, 85%, and 85%, respectively. In the TAE group, the corresponding rates were 68%, 37%, and 0. In our study, we evaluated the treatment with TAE first, and then PEI proved effective in the treatment of patients with large HCC lesions, especially with regard to the long-term survival rates.

The combination of TAE and PEI improved the patients' survival, and this combination therapy should therefore be considered as an appropriate treatment for patients with large encapsulated HCC lesions.

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