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CLINICAL INVESTIGATION

Necrosis and Apoptosis in Hepatocellular Carcinoma Following Low-Dose Versus High-Dose Preoperative Chemoembolization

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Abstract Our purpose was to study necrosis and apoptosis of hepatocellular carcinoma (HCC) cells after preoperative transcatheter arterial chemoembolization (TACE) with use of low-dose and high-dose anticancer drugs in HCCs. Fifty-four patients with advanced but surgically resectable HCC were studied. Thirty-four patients who elected to undergo preoperative superselective TACE were randomized to low- and high-dose TACE. Patients in group A ($n = 16$) received low-dose anticancer drugs: 2 mg mitomycin C (MMC), 10 mg epirubicin (EPI), and 100 mg carboplatin (CBP). Patients in group B ($n = 18$) were given high doses of anticancer drugs (10 mg MMC, 40 mg EPI, and 300 mg CBP). Hepatic resection was subsequently performed. Group C comprised 20 patients who underwent resection without TACE. In all patients the necrosis rates and apoptosis index of tumor cells were evaluated by pathologic examinations and terminal deoxynucleotidyl transferase–mediated nick-end labeling assay. There was no significant difference between group A and group B in tumor response ($p > 0.05$) after TACE. Necrosis rates in groups A, B, and C were $88.4 \pm 11.1\%$, $87.1 \pm 12.5\%$, and $7.3 \pm 3.5\%$, respectively. There was no significant difference between group A and group B ($p > 0.05$), while statistical difference was found between group A and group C ($p < 0.001$) and between group B and group C ($p < 0.001$). Apoptosis indexes in the three groups were $11.0 \pm 4.0\%$, $10.7 \pm 3.9\%$, and $5.6 \pm 2.6\%$, respectively. Statistical difference exhibited between group A and group C ($p < 0.001$) and group B versus group C ($p < 0.001$). No significant difference was observed between group A and group B ($p > 0.05$). In conclusion, superselective TACE with low- and high-dose chemotherapeutic agents induced similar degrees of cellular apoptosis and necrosis.

Keywords Carcinoma, hepatocellular · Chemoembolization, therapeutic · Dose-response relationship, drug · Evaluation studies

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Introduction

Transcatheter arterial chemoembolization (TACE) is the most widely used therapy for unresectable hepatocellular carcinoma (HCC). It is reported that the tumor necrosis rate after TACE is about 95–100% in 20–70% of cases [1–3]. Several nonrandomized studies have demonstrated a beneficial effect of TACE on survival. This result has not been confirmed with randomized trials [4–6]. The real benefit of anticancer drugs on survival has been questioned, as some authors have reported favorable results of transcatheter arterial embolization (TAE) without anticancer drug and no significant differences in tumor response and survival among various chemotherapeutic regimens [7–9]. Some studies have shown that TACE or transcatheter arterial infusion (TAI) with use of low-dose anticancer drugs could also achieve a satisfactory effect in the treatment of advanced HCC [10, 11]. In this study, we investigated the pathologic changes including apoptosis index and necrosis rate after preoperative chemoembolization with high-dose vs. low-dose anticancer drugs in resectable HCCs. Both high-dose and low-dose anticancer drug regimens have

been reported in clinical practice [12, 13]. A variety of differing protocols, employing different drugs, combinations, and doses, has been used for TACE [7–13]. The purpose of the study was to compare the anticancer effects of two different drug dose regimens in patients with HCC. The purpose of the study was to compare the anticancer effects of two different regimens (different dosage of anticancer drugs) in patients with HCCs. The idea is to extrapolate the findings to situations in which the patients have unresectable malignant tumors and therefore turn to TACE instead of surgery.

Materials and Methods

Patient Diagnosis and Grouping

Between January 2000 and May 2004, 54 patients with resectable HCC admitted to Nanfang Hospital, Southern Medical University, Guangzhou, China, were enrolled in the study. This study was approved by the hospital review board and the hospital ethics committees. The series included 49 men and 5 women, with an average age of 49.1 years (range, 24–68 years). Diagnosis of HCC was confirmed by two imaging studies (computed tomography [CT] and magnetic resonance imaging [MRI]) with increased α-fetoprotein (AFP) levels (>400 ng/ml). Tumor biopsy was performed in cases in which imaging findings were not consistent with features characteristic of HCC or when levels of tumor markers were not elevated. Patients with Child–Pugh C disease (according to Child–Pugh classification), TNM stage IV, or presence of portal vein thrombosis, vascular invasion, portosystemic shunts, hepatofugal flow, or extrahepatic metastasis were excluded. The patients themselves could decide whether to undergo preoperative TACE or proceed directly to surgical resection, on the basis of informed consent. A total of 34 patients elected to receive preoperative TACE, and these patients were randomly divided into two groups using a computer random number generator. In group A, 16 patients received low-dose anticancer drugs: 2 mg mitomycin C (MMC), 10 mg epirubicin (EPI), and 100 mg carboplatin (CBP). Patients in group B ($n = 18$) all underwent TACE with high-dose anticancer drugs (10 mg MMC, 40 mg EPI, and 300 mg CBP). The remaining 20 patients were treated with resection alone (group C) and served as the control. Liver function before treatment was evaluated using the Child–Pugh classification. There were 48 patients with Child class A disease, and 6 with Child class B disease in this series. By TNM, 5 patients were classified as stage I, 34 as stage II, and 15 as stage III. The average maximum diameter of the main tumor was 7.98 cm (<5 cm in diameter in 8 cases, 5–8 cm in 17 patients, and >8 cm in 29 patients). Patients' characteristics assessed just before the initial TACE are reported in Table 1. There were no significant differences among the three groups in background factors such as age, gender, AFP level, tumor progression, and underlying liver function.

TACE

In all patients in groups A and B, Seldinger technique was used to access the right common femoral artery. Initially, celiac and superior mesenteric angiography was performed, followed by arterial portography via the superior mesenteric or splenic artery. Following conventional hepatic angiography, a vascular catheter was inserted superselectively into the hepatic artery that fed the tumor. Coaxial microcatheters were used in about 45% of the procedures when a stenotic or tortuous hepatic artery was present. After the tumor feeding arteries were catheterized, the anticancer drugs were dissolved in sterile contrast (Iopamidol, Bracco, Italy) and then emulsified in lipiodol (Savage, USA) at a 1:1 ratio. The volume of the lipiodol administered in any one session depended on the size and vascularity of the territory treat, and ranged from 5 to 22 ml. The emulsion was slowly injected under fluoroscopic control, thus making it possible to discontinue the injection in the case of retrograde flow. The feeding arteries of tumors were then embolized by polyvinyl

Table 1 Baseline characteristics of patients and treatment parameters for the three groups ($n = 54$)

Characteristic	Group A ($n = 16$)	Group B ($n = 18$)	Group C ($n = 20$)	p value
Gender (M/F)	15/1	16/2	18/2	NS
Age (year)	51.5 ± 9.2	49.0 ± 12.3	47.3 ± 15.4	NS
AFP (U/ml)	2,678 (5–10,000)	2,429 (3–15,000)	2,979 (15–40,000)	NS
Tumor size (cm)	7.97 ± 2.07	8.09 ± 1.95	7.89 ± 1.98	NS
Child–Pugh (A/B)	14/2	16/2	18/2	NS
TNM stage (I/II/III)	1/11/4	2/11/5	2/12/6	NS
Lipiodol used (ml)	11 (4–22)	11 (5–20)	–	NS
No. of TACE treatments	1 (1–3)	1 (1–4)	–	NS
Duration, last TACE to op (days)	17.0 ± 5.6	19.0 ± 6.8	–	NS

Note: NS, not significant

alcohol (PVA) particles (sphere size, 300–500 μm; Boston Scientific) until the arterial blood flow stopped. A second preoperative TACE was performed 1 month after the first TACE. The end point was regarded as one of the following: (1) the plasma AFP level had decreased by at least 30%; (2) the average diameter of the main tumor had decreased by at least 25% (compared with that seen on previous imaging) on the CT scan performed 4 weeks later; and (3) the main supplying arteries were occluded and other collateral circulation could not be identified or catheterized. Resections were performed after a mean delay of 18 (range, 7–35) days after the last TACE. There was no significant difference between group A and group B in dose of lipiodol used, number of embolization procedures, or duration between last TACE and operation ($p > 0.05$) (Table 1).

Evaluation of Tumor Response

In groups A and B, CT was always performed before TACE and after the last TACE. Tumor size was measured prospectively by CT scan before the TACE and by postoperative pathology. The changes in average diameter of the tumor were compared in the two groups. In group C, we measured the tumor size on the initial diagnostic CT and compared it with that of the resected specimen. Serum AFP levels were evaluated before TACE and after the last TACE in groups A and B. Changes in AFP level were compared.

Evaluation of Necrosis Rate

Resected tumor specimens were collected in all patients. The scale of area of necrosis was assessed by both macroscopy (cross section) and focused microscopy (hematomylin & eosin stain; HE) examination. In macroscopy examination, necrotic areas appeared black, sharly demarcated, dry, and shriveled. Under microscopy, necrotic areas were defined as having a loss of architecture and staining pink with HE. Necrotic cells did not retain their cellular outlines. We tried to calculate the necrotic area by measuring the midcoronal and midsagittal diameters. Necrotic areas were traced and planimetered on each slice, and the results were summed to calculate the ratio of total necrotic area. The diameters of tumors of the specimens were compared with those before TACE in groups A and B. The necrosis rate (percentage of necrosis area in tumor) and number of cases of complete necrosis in group A were compared with those in group B.

Evaluation of Apoptosis Index

Terminal deoxynucleotidyl transferase–mediated nick-end labeling (TUNEL) assay was used to evaluate apoptosis index in all specimens except when total necrosis was found by microscopic examinations. TUNEL assay was performed using the In situ Cell Death Detection Kit (Roche Diagnostics) according to the manufacturer's instructions. Five areas were selected under light microscopy, and apoptosis of these areas was counted per high-power field (400×) [14]. The apoptosis index (%) = [(number of apoptosis cells/number of counted cells) × 100%] was calculated for each specimen.

Statistical Analysis

SPSS 10.0 software (SPSS, Chicago, IL, 1999) was used for statistical analysis. Chi-square test, Fisher's exact probability test (two sided), and Wilcoxon signed-rank test (two sided) were used for comparison of background factors among the three groups. Student's *t*-test (two tailed) was adopted for determination of the tumor response in each group. Wilcoxon signed-rank test (two related samples) was used for changes in serum AFP level, and one-way ANOVA for comparison of necrotic rate and apoptosis index among the three groups. Differences were considered statistically significant when the p value was <0.05.

Results

Tumor Response

The average changes in tumor size in groups A and B are listed in Table 2. There was no significant difference between group A and group B, between group B and group C, or between group A and group C in tumor size before TACE. Preoperative TACE resulted in a statistically significant decrease in tumor size in both group A and group B ($p < 0.001$ respectively), and there was no significant difference between group A and group B in tumor response ($p = 0.894$). The tumor size before and after resection in

Table 2 Tumor response after TACE in groups A and B

Group	*n*	Diameter of tumor (cm)		Before vs. after TACE	
		Before TACE	After TACE	*t*	*p*
A	16	7.97 ± 2.07	6.39 ± 1.72	4.875	0.000
B	18	8.09 ± 1.95	6.32 ± 1.62	5.198	0.000
A vs. B		$F = 0.053$, $p = 0.852$	$F = 0.018$, $p = 0.894$		

Table 3 Comparison of necrosis rates and apoptosis indexes in the three groups

Group	Necrosis			Apoptosis	
	n	Necrosis rate	Cases of total necrosis	*n*	Apoptosis index (%)
A	16	88.4 ± 11.1%	4 (25%)	12	11.0 ± 3.98%
B	18	87.1 ± 12.5%	4 (22%)	14	10.7 ± 3.94%
C	20	7.3 ± 3.5%	0	20	5.6 ± 2.6%
All		$F = 439.851$, $p = 0.000$	–		$F = 14.102$, $p = 0.000$
A vs. B		$F = 0.115$, $p = 0.736$	$p = 1.000$[a]		$F = 0.008$, $p = 0.963$
A vs. C		$F = 960.642$, $p = 0.000$	_		$F = 24.119$, $p = 0.000$
B vs. C		$F = 751.425$, $p = 0.000$	_		$F = 22.494$, $p = 0.000$

[a] Fisher's exact test

group C was 7.89 ± 1.98 and 7.94 ± 2.00, respectively. There was no significant change in tumor size in group C ($t = 0.292$, $p = 0.774$), while a statistically significant difference was found between group A and group C ($F = 5.996$, $p = 0.020$) and between group B and group C ($F = 10.341$, $p = 0.003$) after TACE. Mean serum AFP level was significantly decreased in group A (from 2678 to 954 μg/L; $Z = -3.237$, $p = 0.001$) and group B (from 2429 to 878 μg/L; $Z = -3.432$, $p = 0.001$).

Necrosis Rates and Apoptosis Indexes

Necrosis rates and apoptosis indexes of the three groups are listed in Table 3. Necrosis rates in the three groups were 88.4 ± 11.1%, 87.1 ± 12.5%, and 7.3 ± 3.5%, respectively. There was no significant difference between group A and group B ($F = 0.115$, $p > 0.05$), while a significant difference was found between group A and group C ($F = 960.642$, $p < 0.001$) amd between group B and group C ($F = 751.425$, $p < 0.001$). Total necrosis was found in four cases in group A (25%) and four cases (22%) in group B. No significant difference was exhibited (Fisher's exact test, $p = 1.000$).

The average apoptosis indexes in the three groups were 11.0 ± 4.0%, 10.7 ± 3.9%, and 5.6 ± 2.6%, respectively. A statistically significant difference was exhibited between group A and group C ($F = 24.199$, $p < 0.001$) and between group B and group C ($F = 22.494$, $p < 0.001$). No significant difference was observed between group A and group B ($F = 0.008$, $p > 0.05$) (Figs. 1–8).

Discussion

TACE is a common treatment for patients with unresectable HCC. TACE often consists of the injection of a lipiodol-anticancer drug emulsion into the tumor's feeding arteries, followed by particulate embolization. Bland embolization with particles alone can cause tumor ischemia, depriving it of

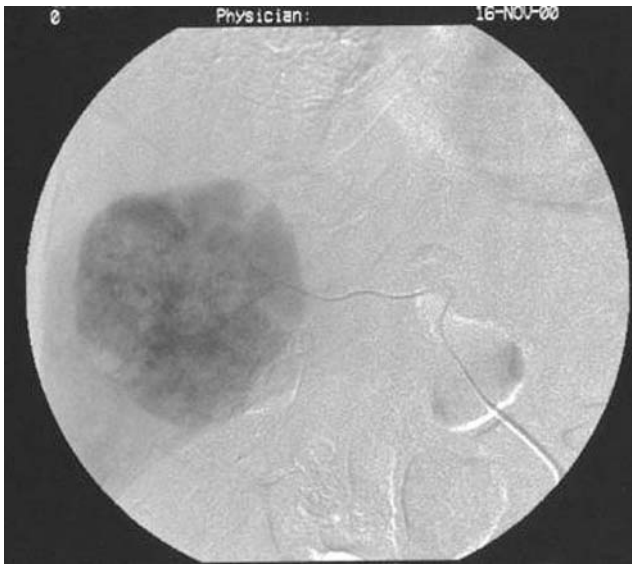

Fig. 1 Hepatic arterial angiography of a 55-year-old man with HCC. An apparent tumor stain can be seen in the right lobe during the parenchymal phase

nutrients and oxygen, and result in tumor cell necrosis and apoptosis. Therefore it can control tumor growth while preserving as much functional liver tissue as possible [4, 9, 15, 16]. When chemotherapy is added, tumor drug concentrations in the tumor are one to two orders of magnitude greater than can achieved by infusion alone, and the dwell time of the chemotherapy agent is markedly prolonged [17]. In several studies the tissue levels of chemotherapy agents were found to be up to 40 times higher in the tumor than in the surrounding liver, and to persist for several months [18–20]. Many previous studies have found improved therapeutic effects with more extensive necrosis of the HCC in patients who received chemoembolization rather than bland embolization [21]. However, the effect upon survival of TACE is still controversial, despite the high tumor response rate.

Consensus is lacking about the most suitable dosage of anticancer drugs in TACE. High dosages of anticancer drugs are typically used in TACE in China, Korea, and

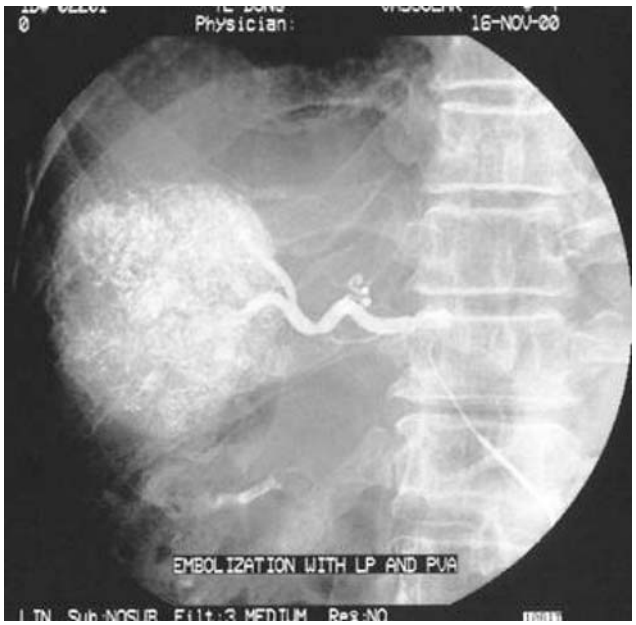

Fig. 2 Superselective chemoembolization was performed with a lipiodol/anticancer drug emulsion (low dose) followed by PVA embolization. Lipiodol is seen deposited in the tumor on digital spot radiograph

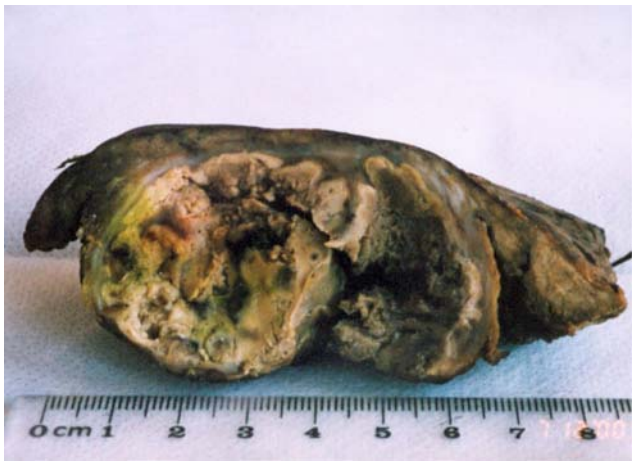

Fig. 3 After resection, large-scale necrosis is found on the cut surface of the specimen

other Asian countries. In China, the conventional dosages of anticancer drugs used in TACE are 10–30 mg MMC, 60–120 mg cisplatin (CDDP) or 200–400 mg CBP, 30–60 mg adriamycin (ADM) or 30–100 mg EPI, 1000–1500 mg 5-FU. Combination of three or four drugs is common in one procedure. Nevertheless, in Western countries as well as Japan, a much lower dosage is used [10, 22–24]. Despite marked antitumor responses, TACE with high-dose anticancer drugs may also have deleterious effects on hepatic function and lead to compromise of the immune system, thus impairing the baseline prognosis [25–27]. In our study, 100 mg CBP was used in the

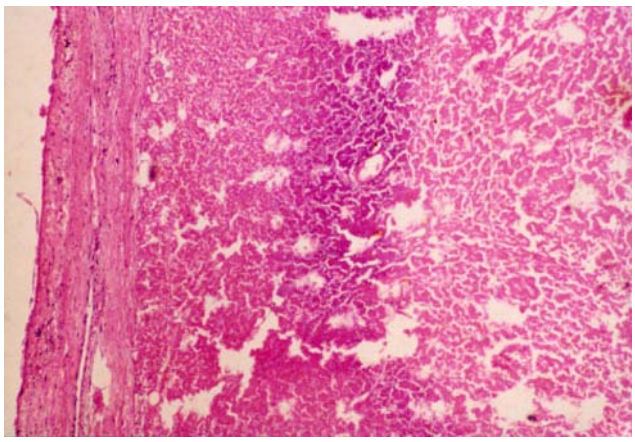

Fig. 4 Extensive necrosis of HCC tissue is seen under microscopy. (HE; original magnification, 100×)

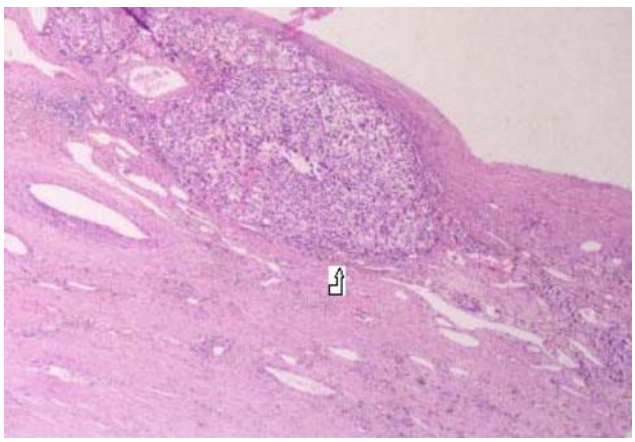

Fig. 5 Residual tumor cells (arrow) are found inside the pseudocapsule. (HE; original magnification, 100×)

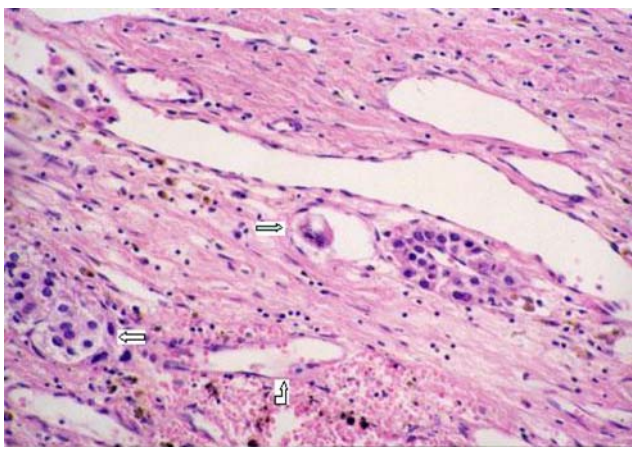

Fig. 6 A small supplying vessel (angled white arrow) still exists beside the tumor nest (straight white arrow). Small tumor emboli (green arrow) can be seen within the small vessel. (HE; original magnification, 200×)

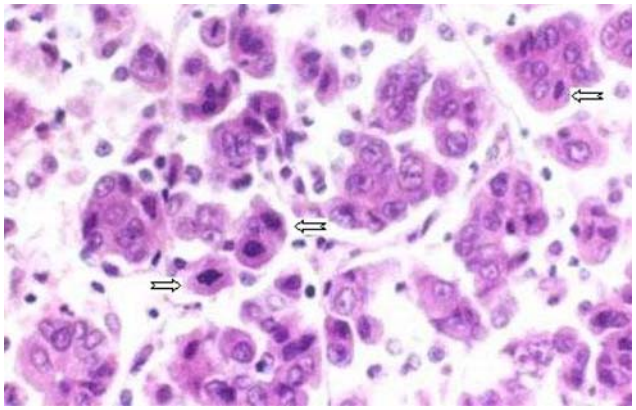

Fig. 7 Many apoptotic cells (straight white arrows) are detected with HE stain. (Original magnification, 400×)

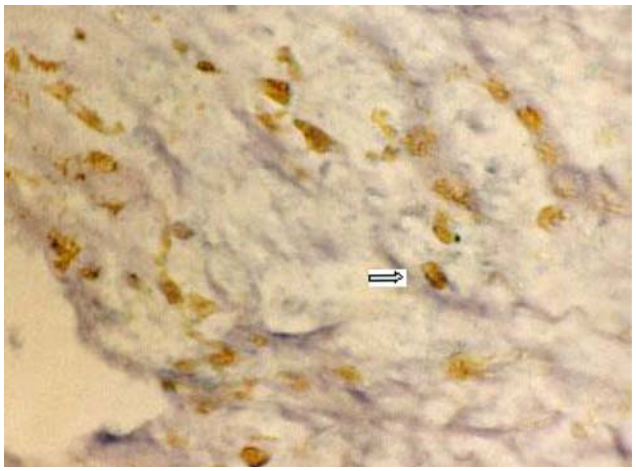

Fig. 8 Apoptosis of HCC cells (green arrow) is demonstrated by TUNEL assay

low-dose group, and 300 mg in the high-dose group. We thought 100 mg CBP should be the low-dose regimen, as the conventional dose of CBP is 200–400/m^2 for systemic chemotherapy, which is different from the conventional dose of CDDP, which was 80–100 mg/m^2.

Some authors have reported favorable results of TACE with low-dose anticancer drugs. Kamada et al. [10] introduced low-dose CDDP (41 mg) in TACE for treatment of HCC, and the survival rates were 81%, 41%, 19%, and 13% for 1, 3, 5, and 7 years, respectively. Maeda et al. [11] reported that TACE with low-dose cisplatin had an excellent anticancer effect and improved the survival rate for patients with HCC to 29.6% at 5 years. Sumie et al. [28] reported that hepatic arterial infusion with low-dose CDDP and 5-FU had a better antitumor effect than TACE and may be a useful therapeutic option for more advanced HCC. We have also shown, in our previous study, that TACE with use of high-dose anticancer drugs did not significantly increase survival rate compared with TACE with low-dose anticancer drugs, and the dosage of anticancer drugs employed in TACE was not relevant to the survival rates [12]. Regarding side effects, we reported in our previous study that postembolization syndromes such as nausea, vomiting, fever, and abdominal pain were more severe in the high-dose group than in the low-dose group when evaluated by Southwest Oncology Group Criteria. Moreover, deterioration of liver function was more serious in the high-dose than in the low-dose group [12, 13]. In this study, TACE with high-dose anticancer drugs did not result in irretrievable toxicities to liver. Liver function recovered 2 weeks after the procedures in all patients.

In this study, we compared the effect of high- and low-dose TACE on liver tumors at macroscopic and microscopic levels. We found that there was no significant difference between the low-dose and the high-dose groups in TACE-induced decreases in tumor size, cell necrosis rates, and apoptosis indexes. Not surprisingly, statistical differences were exhibited when both TACE groups were compared with the surgical control group (group C). Therefore, we believed that TACE using a low-dose anticancer drug(s) has the same anticancer effects as TACE with high-dose anticancer drugs.

Up to now, most studies have used imaging criteria and survival to assess the effectiveness of TACE regimens. Pathologic assessment including apoptotic index and necrosis rate were rarely used to evaluate the effects of TACE. Xiao et al. [29] reported that the apoptotic index in HCC cells was significantly higher in the preoperative TACE group than the non-TACE group; they also found that preoperative TACE regimens may enhance apoptosis of HCC cells by up-regulating the expression of Bax protein and down-regulating the expression of Bcl-2 protein and ratio of Bcl-2-to-Bax protein expression.

In our study, apoptosis was evaluated 18 days after TACE. Apoptotic changes can be detected within 48 h, especially in vitro. Still, it can prove impractical to resect the tumor within 2 days after TACE, because of postembolization syndrome and potential acute deterioration of liver function, which can occur in some patients immediately after TACE. Apoptotic changes can be evaluated (using the TUNEL method) 21 days after management of HCC [30]. Kemal et al. [31] observed apoptotic changes in renal tubular cell injury induced by hyperoxaluria at 21 and 42 days (7 and 28 days after management). Wang et al. [32] reported that the apoptosis index in HCC was significantly higher in the TAI group (14 days after treatment) than in the control group. We chose to evaluate the apoptosis index at 18 days after TACE because of the demonstration of apoptosis detection in similar time frames.

This study has several limitations. These include the small number of patients; the population of patients, which differs from that in whom TACE is typically used (patients

with tumors suitable for surgery); the lack of control for the potential impact of particulate embolization on cell death and apoptosis; and the lack of survival data.

In conclusion, we have shown, in a small prospective randomized controlled study, that preoperative TACE can cause extensive tumor necrosis, induce apoptosis of tumor cells, and result in significant shrinkage of tumor size. Low-dose and high-dose TACE had equivalent effects on HCC in terms of reduction in tumor size, tumor necrosis, and induction of apoptosis. These results suggest that superselective TACE with low-dose anticancer drugs is feasible and effective and, arguably, could be advocated. Further large-scale multicenter trials will be needed to further define more effective anticancer drugs, regimens, and optimal dosages.

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