Kaohsiung Journal of Medical Sciences (2011) 27, 431–436

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ORIGINAL ARTICLE

Risk factors for the leakage of chemotherapeutic agents into systemic circulation after transcatheter arterial chemoembolization of hepatocellular carcinoma

Ming-Yen Hsieh [a], Zu-Yau Lin [b,c,d,*], Su-Hwei Chen [e], Wan-Long Chuang [b,d]

[a] *Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan*
[b] *Division of Hepatobiliary Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[c] *Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[d] *Department of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[e] *Faculty of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan*

Received 12 November 2010; accepted 13 January 2011
Available online 26 July 2011

KEYWORDS
Epirubicin;
Hepatocellular carcinoma;
Mitomycin C;
Plasma concentration;
Transcatheter arterial chemoembolization

Abstract This prospective study was to investigate the possible risk factors for the leakage of chemotherapeutic agent into the systemic circulation after transcatheter arterial chemoembolization (TACE) of hepatocellular carcinoma (HCC). Peripheral plasma concentrations of chemotherapeutic agents were determined at 1 hour and 72 hours after TACE by high-performance liquid chromatography in 53 patients. HCC were divided into three types namely single nodule (<5 cm), multiple nodules (all <5 cm), and main nodule measuring 5 cm or more. Forty-four patients (83%) showed detectable chemotherapeutic concentrations within 72 hours after TACE. Patients with single nodular-type HCC had lower incidence of detectable plasma chemotherapeutic agents after TACE than the other two groups (all $p < 0.05$). The injected doses of lipiodol, epirubicin, and mitomycin C were lower in patients without detection than in patients with detectable chemotherapeutic agents (all $p < 0.05$). Multivariate logistic regression showed that tumor type and injected dose of lipiodol were two independent risk factors for the leakage of mitomycin C at 1 hour after TACE (all $p < 0.05$), and the injected dose of mitomycin C was the risk factor for the leakage of epirubicin at 1 hour after TACE ($p < 0.05$). In conclusion, multiple nodular type and large nodule measuring 5 cm or more have a risk of leakage of mitomycin C after TACE. Injected dose of lipiodol and mitomycin C as risk

* Corresponding author. Cancer Center and Division of Hepatobiliary Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, No. 100 Tzyou 1st Road, Kaohsiung 807, Taiwan.
E-mail address: linzuyau@yahoo.com.tw (Z.-Y. Lin).

doi:10.1016/j.kjms.2011.06.001

factor for the leakage of mitomycin C and epirubicin respectively may be because of competition of their injected volume within the limited space of target.

Introduction

Transcatheter arterial chemoembolization (TACE) is a palliative method for the management of hepatocellular carcinoma (HCC) [1—3]. However, the optimal schedule, best anticancer agent, and best technique for TACE are still unclear [3—5]. Several embolic agents have been used in TACE. Although lipiodol [5—7] and absorbable gelatin sponge or starch microspheres [8,9] have been applied in TACE, there is no strong evidence to show the advantage of these agents to delay the clearance of chemotherapeutic agent from the liver after TACE. Application of nonabsorbable polyvinyl alcohol microspheres as the embolic agent in TACE was also reported of no influence on the reduction in the systemic toxicity of chemotherapeutic agent in liver metastases [9,10]. On the other hand, chronic hepatitis B and C viral infections are two major etiologies in developing HCC [11,12]. Flare-up of hepatitis because of reactivation of hepatitis B or hepatitis C virus is a well-known complication in patients with malignant disease who receive chemotherapy [13,14]. Although TACE is not a systemic chemotherapy, there are evidences showing the influence of TACE on replication of hepatitis B or hepatitis C virus [15—18]. Moreover, the plasma concentrations of the leaked chemotherapeutic agents after TACE may not be enough to exert their chemotherapeutic effects on the residual cancer cells. This may increase the risk of chemotherapeutic resistance of the residual cancer cells. Therefore, understanding the risk factors for the leakage of chemotherapeutic agent after TACE is very important in long-term management of these patients. The purpose of this prospective study was to investigate these risk factors, which had not been clarified in the previous studies.

Patients and methods

Patients

From February 2008 to February 2009, a total of 53 patients with HCC who planned to receive TACE were included (Table 1). The diagnosis of HCC was based on fine-needle aspiration cytology and/or biopsy. HCC were divided into three types namelysingle nodule (<5 cm), multiple nodules (all <5 cm), and main nodule measuring 5 cm or more with or without daughter nodules. For 17 patients with single nodule of HCC, 10 patients received further local ablation therapy and 1 patient received operative resection at least 1 week after TACE. The remaining six patients refused operative resection or local ablation therapy because of their personal reasons. The diagnosis of arterioportal shunt was based on the pre-TACE angiography and was made by a radiologist. The patients with large arterioportal shunts, which needed to be particularly treated by implantation of various sizes of Nester embolization coils (Cook, Inc., Bloomington, IN, USA), were excluded. None of the patients had shunts communicating with the hepatic arterial system and the hepatic venous system. The diagnosis of liver cirrhosis was based on a coarse and contracted liver on abdominal sonography with at least one of the following two positive findings, including (1) esophageal or cardiac varices found by endoscopic examination and (2) presence of portal collateral circulation with or without splenomegaly on computed tomography. Chronic hepatitis B or hepatitis C was diagnosed by positive serum hepatitis B surface antigen or antihepatitis C antibody for more than 6 months. This study was approved by the Institutional

Table 1 Characteristics of three groups of patients with hepatocellular carcinoma

Characteristics	Single nodule (<5 cm)	Multiple nodules (all <5 cm)	Main nodule ≥5 cm with or without daughter nodules	Total
Patients, *n*	17	24	12	53
Sex (M/F)*	14/3	16/8	9/3	39/14
Age (y)*	56 (37—76)	70 (50—85)	62.5 (44—78)	63 (37—85)
Etiology*				
Chronic hepatitis B	8	8	6	22
Chronic hepatitis C	8	16	5	29
Unknown	1	0	1	2
Cirrhosis (±)**	9/8	20/4	11/1	40/13
Child-Pugh class (A/B)*	8/1	17/3	9/2	34/6
Arterioportal shunt (±)*	2/15	4/20	4/8	10/43

Data are given as the median and range.
The Kruskal-Wallis test or Chi-square test was applied for statistical analysis.
*$p > 0.05$; **$p < 0.05$.

Review Board of our hospital. Each patient gave informed consent to participate in this study.

Methods

Procedure of TACE

TACE was carried out by infusion of the mixture of chemotherapeutic agents and lipiodol (Lipiodol Ultra-Fluid; Guerbet, Aulnay-sous-Bois, France) into the lesion followed by embolization of the supplying arteries using various sizes of nonabsorbable Embosphere microspheres (BioSphere Medical, Inc., Rockland, MA, USA), or absorbable agents (Avitene Microfibrillar Collagen Hemostat; MedChem Products, Inc., Woburn, MA, USA), or gelfoam particles of 1–2 mm in size (Pharmacia & Upjohn Company, Kalamazoo, MI, USA). Selection of nonabsorbable or absorbable embolic agent was based on the size of the tumor and the patterns of the supplying arteries and was decided by both the radiologist and patient because only gelfoam could be paid by the national health insurance. Fifty-one patients received both epirubicin (Pharmacia & Upjohn S.p.A, Milan, Italy) and mitomycin C (Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) as chemotherapeutic agents and 2 patients received epirubicin alone. Each vial of chemotherapeutic agent (epirubicin 10 mg/vial, mitomycin C 2 mg/vial) was dissolved by 2 mL contrast medium (Ultravist; Bayer Schering Pharma AG, Berlin, Germany). The desired doses of chemotherapeutic agents and lipiodol in separate syringes were well mixed by a connector before injecting into the lesion. The doses of chemotherapeutic agents and lipiodol were decided by the radiologist based on the following criteria. The dose of total injected lipiodol depended on the sum of the diameters of target nodules (1 mL lipiodol for 1 cm diameter). The maximum dose of lipiodol was 10 mL in each session of TACE. The estimated volume of total injected chemotherapeutic agents was twice of lipiodol volume. However, the actual injected volume of chemotherapeutic agents could be reduced because of the condition of the patient, such as presence of leucopenia. To minimize the possible damage of hepatic parenchyma caused by TACE, all patients received superselective procedure for embolization of the tumor. The procedure of TACE was complete when all detectable supplying arteries of the tumor and arterioportal shunt were embolized evidenced by immediate post-TACE angiography. The whole procedure of TACE was carried out by an independent radiologist who did not know the contents of the study. Totally, three radiologists with different experience in TACE procedure (DKW, 19 years; PMCS, 10 years; MLC, 2 years) were involved.

Determination of epirubicin and mitomycin C concentrations in plasma

Plasma concentrations of chemotherapeutic agents (epirubicin and mitomycin-C) were measured at 1 hour and 72 hours after TACE. The plasma used for the study were collected immediately drawn from the peripheral veins of the patients and were stored at −20°C for further investigation. Plasma concentrations of epirubicin and mitomycin C were detected by high-performance liquid chromatography (HPLC) system using Hitachi pump L-2130 and Hitachi UV-Vis detector L-2420 (Hitachi High-Technologies Corp., Tokyo, Japan) with Waters Model 717 Plus HPLC autoinjector (American Instrument Exchange, Inc., Haverhill, MA, USA). Epirubicin was detected at 480 nm wavelength and mitomycin C was detected at 368 nm. The results were analyzed by Hitachi Model D-2000 chromatography Data Station software (Hitachi High-Technologies Corporation, Tokyo, Japan). The detection limits for epirubicin and mitomycin C were all 2 ng/mL. The whole procedure was performed by the same person. The coefficient of variation values for intra-assay (calculation from five measurements) were 3.5% and 7.6% for epirubicin and mitomycin C, respectively.

Statistical analysis

All data for continuous variables were expressed as median and range. Difference of medians was analyzed by the Mann-Whitney U test or Kruskal-Wallis test. Fisher's exact test or Chi-square test was used to compare proportions between groups. Correlation analysis was investigated by the calculation of a correlation coefficient (r). Multivariate logistic regression was applied to investigate the risk factors for leakage of chemotherapeutic agents after TACE. The statistical significance was defined as p value less than 0.05.

Results

Patients with main HCC nodule measuring 5 cm or more received higher injected doses of chemotherapeutic agents and lipiodol than the other two groups of patients (Table 2). The injected doses of lipiodol were lower in patients with single nodule of HCC than in patients with multiple nodules of HCC. Plasma epirubicin and mitomycin C were detected at 62.3% ($n = 33$, 7.2 ng/mL and 2.2–65.8 ng/mL) and 64.7% ($n = 33$, 4.8 ng/mL and 2.6–19 ng/mL), respectively at 1 hour after TACE, and 15.1% ($n = 8$, 16.7 ng/mL and 6.1–32.2 ng/mL) and 2% ($n = 1$, 4.8 ng/mL), respectively at 72 hours after TACE (Fig. 1A and B). Overall, 44 patients (83%) showed detectable plasma epirubicin and/or mitomycin C concentrations within 72 hours after TACE (Table 3). Patients with single nodular-type HCC had significant lower incidence of detectable plasma chemotherapeutic agents than the other two groups of patients. The injected doses of lipiodol, epirubicin, and mitomycin C were significantly lower in patients without detection than in patients with detectable plasma chemotherapeutic agents. Plasma epirubicin and mitomycin C concentrations at 1 hour after TACE showed positive correlation with their corresponding injected doses ($r = 0.44$, $p < 0.01$ for epirubicin; $r = 0.47$, $p < 0.001$ for mitomycin C). Plasma epirubicin concentrations at 72 hours after TACE also showed positive correlation with their corresponding injected doses ($r = 0.4$, $p < 0.01$) and their corresponding plasma concentrations at 1 hour after TACE ($r = 0.31$, $p < 0.05$). Tumor type, injected doses of chemotherapeutic agents and lipiodol, lipiodol/contrast medium ratio, presence of arterioportal shunt, using absorbable or nonabsorbable embolic agent and doctors with different experience were used as items in multivariate logistic regression. Tumor type ($p < 0.05$) and

Table 2 The injected doses of chemotherapeutic agents and lipiodol in three groups of patients with hepatocellular carcinoma

Chemotherapeutic agents	Single nodule (<5 cm)	Multiple nodules (all <5 cm)	Main nodule ≥5 cm with or without daughter nodules	Total
Injected epirubicin (mg)	10*** (2—20)	10*** (2.5—20)	20*** (10—30)	10 (2—30)
Injected mitomycin C (mg)	2** (0.4—4)	2* (0.5—4)	4* (1—6)	2 (0.4—6)
Lipiodol (mL)	2.5**** (1.5—4)	5**** (2—10)	7.5**** (3—10)	4 (1.5—10)
Lipiodol/contrast medium ratio	0.75 (0.5—2.5)	0.85 (0.5—2.67)	0.83 (0.5—2.5)	0.83 (0.5—2.67)

Data are given as the median and range.
The Kruskal-Wallis test, Mann-Whitney test, or Chi-square test was applied for statistical analysis.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

injected dose of lipiodol ($p < 0.05$) were two independent risk factors for the leakage of mitomycin C at 1 hour after TACE, and the injected dose of mitomycin C ($p < 0.05$) was the risk factor for the leakage of epirubicin at 1 hour after TACE investigated by multivariate logistic regression.

Five patients (9.4%) showed increasing plasma epirubicin (four patients) or mitomycin C (one patient) concentrations at 72 hours after TACE (Fig. 1A and B) (Table 4). Patients with main HCC nodule measuring 5 cm or more had significantly higher incidence of increasing plasma epirubicin or mitomycin C concentrations at 72 hours after TACE than patients with other types of HCC (4/12 *vs.* 1/41, $p < 0.01$). Patients with arterioportal shunt also had significantly higher incidence of increasing plasma epirubicin or mitomycin C concentrations at 72 hours after TACE than patients without arterioportal shunt (3/10 *vs.* 2/43, $p < 0.05$). Multivariate logistic regression using tumor type and presence of arterioportal shunt as items showed that presence of arterioportal shunt might be the risk factor for increasing plasma chemotherapeutic agents at 72 hours after TACE ($p = 0.0718$).

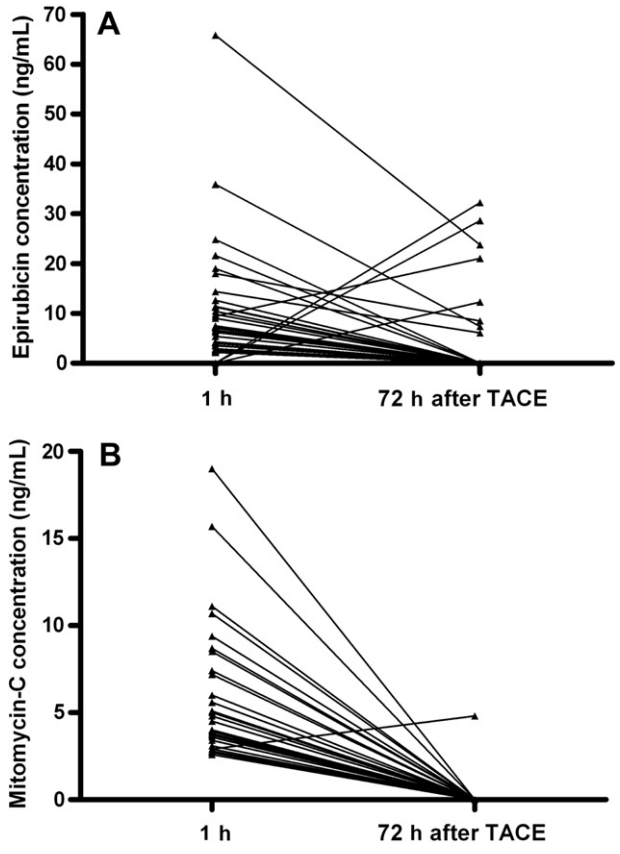

Figure 1. Plasma concentrations of (A) epirubicin and (B) mitomycin-C at 1 hour and 72 hours after TACE of hepatocellular carcinoma. TACE = transcatheter arterial chemoembolization.

Discussion

The present results showed high incidence of leakage of injected chemotherapeutic agents within 72 hours after TACE. Leakage mainly occurred soon after TACE. Afterward, the plasma concentrations of leaked chemotherapeutic agents decreased gradually. Because the systemic circulated mitomycin C has very short half-life, most patients showed undetectable peripheral plasma concentrations of mitomycin C at 72 hours after TACE. Therefore, we applied data obtained 1 hour after TACE to investigate the risk factors for the leakage of chemotherapeutic agents after TACE. The present results showed that the tumor type and the injected doses of lipiodol were two independent risk factors for the leakage of mitomycin C at 1 hour after TACE. The vascularity of HCC usually will increase with increasing tumor size [19]. This indicates that the tumor-related draining venous system is more prominent in larger HCC than in smaller HCC. The injected chemotherapeutic agents thus had higher probability to leak out in larger HCC measuring more than 5 cm than in single nodular-type HCC. On the other hand, embolization of multiple nodules of HCC usually needed to inject chemotherapeutic agents to different parts of the liver. This also will increase the probability to leak out the injected chemotherapeutic agents to systemic circulation. Therefore, patients with multiple nodular-type HCC had higher incidence of leakage of injected chemotherapeutic agents than patients with single nodular-type HCC. Because lipiodol cannot absorb chemotherapeutic agents, injection of lipiodol may compete with the injected volume of chemotherapeutic agents within the limited space of target and thus become a risk factor for the leakage of mitomycin C. The injected dose of mitomycin C becoming a risk factor for the leakage of epirubicin at 1 hour after TACE may also be because of competition of their injected volume within the limited space of target. The new drug-eluting microspheres, which can absorb chemotherapeutic agents,

Table 3 Comparison between patients with or without detectable plasma epirubicin and/or mitomycin C concentrations within 72 hours after TACE for hepatocellular carcinoma

Characteristics	Detectable ($n = 44$)	Undetectable ($n = 9$)
Sex (M/F)	32/12	7/2
Age (y)	67.5 (44—85)	59 (37—80)
Cirrhosis (±)	33/11	7/2
Arterioportal shunt (±)	10/34	0/9
Tumor type		
Single nodule (<5 cm)*	10	7
Multiple nodules (all <5 cm)*	22	2
Main nodule ≥5 cm ± daughter nodules*	12	0
TACE operator (Doctor DKW/PMCS/MLC)	14/21/9	1/7/1
Injected lipiodol (mL)*	4.5 (1.5—10)	2.5 (2—5)
Lipiodol/contrast medium ratio	0.83 (0.5—2.5)	0.93 (0.5—2.67)
Embolic agent		
Nonabsorbable	31	5
Absorbable	13	4
Injected epirubicin (mg)**	17 (2—30)	10 (2.5—10)
Injected mitomycin C (mg)*	2 (0.4—6)	1 (0.5—2)

Data are given as the median and range.
The Mann-Whitney U test, Fisher's exact test, or Chi-square test was applied for statistical analysis.
*$p < 0.05$; **$p < 0.01$.
TACE = transcatheter arterial chemoembolization.

may be a good modality to obliterate these competition effects within the tumor [20]. The reason why the risk factors for the leakage of mitomycin C do not become risk factors for the leakage of epirubicin needs further investigation.

Few patients in the present study had increasing plasma epirubicin or mitomycin C concentrations at 72 hours after TACE. This indicates that the injected chemotherapeutic agents were initially plugged within the lesion and were released subsequently. The present study did not include patients with large arterioportal shunts because these shunts are very difficult to be completely obliterated and leakage of injected chemotherapeutic agents can be expected. However, our result still showed that the presence of small arterioportal shunts, which did not needed to be treated by coil, might be a risk factor for the delay in releasing chemotherapeutic agents into systemic circulation after TACE. This implies that even small arterioportal shunt might have the tendency to rapid recanalization soon after TACE by our method. The new drug-eluting microspheres not only can absorb chemotherapeutic agents but

Table 4 Characteristics of five patients with increasing plasma epirubicin or mitomycin C concentrations at 72 hours after TACE as compared with those at 1 hour after TACE

Patient	1	2	3	4	5
Sex	Male	Male	Female	Male	Male
Age (y)	84	62	51	67	63
Plasma concentration after TACE (ng/mL)					
1 h	2.9 (M)	0 (E)	0 (E)	9.4 (E)	0 (E)
72 h	4.8 (M)	32.2 (E)	28.6 (E)	21 (E)	12.3 (E)
Cirrhosis	Yes	Yes	Yes	Yes	Yes
Arterioportal shunt	Yes	No	Yes	Yes	No
Tumor type	Multiple nodules	M ± N	M ± N	M ± N	M ± N
TACE operator (Doctor)	PMCS	PMCS	MLC	DKW	MLC
Lipiodol/contrast medium ratio	1	1.25	1	0.5	0.83
Embolic agents	Nonabsorbable	Absorbable	Nonabsorbable	Absorbable	Nonabsorbable

E = epirubicin; M = mitomycin C; M ± N = main nodule ≥5 cm with or without daughter nodules; TACE = transcatheter arterial chemoembolization.

also can prevent recanalization of the embolized vessel [21]. This may be a good modality to prevent delay in releasing injected chemotherapeutic agent after TACE. Further study using large number of patients may be necessary to clarify this issue.

In the present study, HCC was classified into three types based on the intrahepatic tumor burden rather than American Joint Committee on Cancer TNM system or other staging systems. This is because that the intrahepatic tumor burden was the main determinant for the injected doses of chemotherapeutic agents, lipiodol, and embolic agent. On the other hand, 24.5% (13/53) patients did not have concomitant liver cirrhosis based on our criteria. Because we did not perform liver biopsy in each patient, the ratio of noncirrhotic patients in the present study might be overestimated. However, this will not influence our results because the factor of arterioportal shunt, which may exist in patients with cirrhosis, is considered in the analysis of data.

The present study indicates that the transient leakage of the injected chemotherapeutic agent into systemic circulation after TACE is very common. Tumor type and injected dose of lipiodol may be risk factors for the leakage of mitomycin C after TACE. High-injected dose of mitomycin C may interfere with the stasis of epirubicin within the tumor and become a risk factor for the leakage of epirubicin after TACE.

Acknowledgment

This work was supported by grants from Kaohsiung Medical University Hospital (KMUH96-6G24 and KMUH96-6G25) and the Department of Health, Executive Yuan, Taiwan, R.O.C. (DOH100-TD-C-111-002). The authors appreciate Jung-San Chang for his help in statistical analysis of the data.

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