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Damage to Liver Function after TACE of Anticancer Drugs in Hepatocellular Carcinoma: Evaluation of Two Kinds of Anticancer Drugs

LU Wei, LI Yan-hao, YU Zhi-jian, HE Xiao-feng, CHEN Yong, ZHAO Jian-bo

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【Abstract】 Objective To study the damage of liver function after transcatheter arterial chemoembolization (TACE) with low-dose versus conventional-dose anticancer drugs in patients with hepatocellular carcinoma (HCC). **Methods** One hundred and twelve patients with unresectable HCC were randomly divided into two groups (A and B) to receive superselective TACE. Low-dose anticancer drugs including mitomycin C (MMC) 2 ~ 8 mg, epirubicin (EPI) 5 ~ 10 mg and carboplatin (CBP) 100 mg were used in group A ($n = 52$), and conventional-dose of anticancer drugs (MMC 10 mg, EPI 40 mg and CBP 300 mg) for patients in group B ($n = 60$). Lipiodol-anticancer drugs emulsion was injected into the feeding arteries of tumor and then followed by embolization of gelatin sponge (GS) or polyvinyl alcohol (PVA) particles. Laboratory examination of the liver function including Child-Pugh scores, total bilirubin (TBIL), albumin (ALB) and alanine aminotransferase (ALT) were evaluated respectively before TACE and at third day, one week and four weeks after this procedure. **Results** In both groups, TBIL, ALT, and Child-Pugh scores increased ($P < 0.001$ or $P < 0.05$) and ALB decreased ($P < 0.001$ or $P < 0.01$) at three days and one week after TACE. Four weeks after-procedure, all the parameters described above showed no significant difference than those before the procedure in group A ($P > 0.05$). On the contrary in group B, a significant difference ($P < 0.05$) was found in the comparison of these parameters (except ALT). **Conclusion** Superselective TACE with low-dose anticancer drugs may induce transient impairment of liver function in the patients with HCC, but those patients used conventional-dose of anticancer drugs frequently cause lasting and more serious worsening of liver function. (J Intervent Radiol, 2006, 15: 351-355)

【Key words】 Carcinoma; Hepatocellular chemoembolization; Therapeutic liver function

Introduction

It is well known that transcatheter hepatic arterial chemoembolization (TACE) can restrict the growth of liver tumors, but it can also cause inevitable damage of liver function. Although the impairment of liver function should be recovered in a short period (about 4 weeks) after TACE, an irreversible hepatic function impairment may present in a considerable amount of patients, particularly in

those patients undertaken several procedures of TACE^[1], or even a few patients may develop acute hepatic function failure and finally cause death by the liver function failure or the cirrhotic complications^[2]. In order to decrease the hepatic impairment, some authors used low-dose anticancer drug in TACE of HCC and showed that a satisfactory effect could also be achieved^[3,4]. In this study, TACE with a low-dose anticancer drug was adopted in one group of patients with HCC, conventional-dose anticancer drug was used in another group of patients with HCC, and then the hepatic function impairment of both groups after TACE was compared.

Authors setting: 510515 Department of Interventional Radiology, Nanfang Hospital, Southern Medical University

Corresponding author: LU Wei

Materials and methods

One hundred and twelve patients were included in this study with male 107 cases and female 5 cases, and aged from 20 to 76 years (mean 49.6 years). In 107 cases, the diagnosis of 39 cases was confirmed by the cytologic finding, and the others were definitively diagnosed by findings of ultrasonography, computed tomography (CT), magnetic resonance imaging, angiography and serum α -fetoprotein (AFP). The underlying hepatic function of this series was established by means of routine biochemical parameters and then was graded according to Child classification^[5] (Child A in 96 cases and Child B in 16). The disease staging of 112 patients was graded according to Okuda classification as follows: Okuda I in 87 cases and Okuda II in 25. In this study, those patients who had surgical indications, serious abnormality of the liver function, main portal vein obstruction or Okuda III staging, were all excluded. Of this series, 112 patients were randomly divided into two groups (A and B) for TACE after routine angiographies. A low-dose drug was used in group A ($n = 52$) as follows: Mitomycin (MMC) 2 ~ 4 mg was used alone if tumor diameter was smaller than 5 cm; MMC 4 ~ 6 mg with Epirubicin (EPI) 5 ~ 10 mg were used if tumor diameter was between 5~8 cm; MMC 6 ~ 8 mg, EPI 10 mg and Carboplatin (CBP) 100 mg were used combinatively if tumor diameter was larger than 8 cm. Sixty cases of the group B were given conventional-dose drugs combinatively including of MMC 10 mg, EPI 40 mg and CBP 300 mg. Superselective arterial infusion of the lipiodol-anticancer drugs emulsion was performed in both groups, and then gelfoam particles or polyvinyl alcohol microsphere were added to embolize the feeding arteries until the blood stream became stagnant. Repeating the procedure of TACE was depended on the findings of CT, AFP and liver function examination etc. Table 1 showed no significant difference in the patients' base-line characteristics and liver function, as well as the embolization approach, lipiodol dose and the times of TACE etc. of both groups, so that the comparative

study of both groups was feasible.

Of this series, the liver function examinations including total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT) and prothrombin time (PT), were carried out before TACE and at 3 days, 1 week and 4 weeks after TACE respectively. Child-Pugh score was determined by the findings of TBIL, ALB, PT as well as the presence of ascites and the stage of encephalopathy. And so the changes of hepatic function of both groups pre-and post-TACE could be well compared.

Results

Total 245 procedures of TACE were done in 112 patients with HCC including once procedure in 42 cases, 2, 3, 4 and 5 times in 37, 19, 9, 5 cases respectively. After the TACE, Child-Pugh score obviously increased at 3 days in both groups, then it decreased apparently at 1 week and recovered to pre-TACE level at 4 weeks in group A, but it decreased gradually at 1 week and kept significant difference in comparing with the score of pre-TACE at 4 weeks in group B. At 4 weeks after TACE, two cases of Child A in the group A dropped to Child B, and one case of Child B to Child C, however in Group B, 5 cases of Child A to Child B and 3 cases of Child B to Child C were present ($P < 0.05$, as seen in table 2).

Child-Pugh score increment pre-TACE of both groups was mainly due to the increased level of TBIL and the decreased level of ALB. The level of TBIL was demonstrated to increase obviously in the early stage after TACE and reached the peak at 3 days. Thereafter, it decreased more rapidly in group A and recovered to the level of pre-TACE at 4 weeks. But in group B it decreased slowly and still higher than that of pre-TACE at 4 weeks. The change of ALT after TACE in both groups was as same as the TBIL; but at 4 weeks, it recovered to the level of pre-TACE.

Comparing with the level of pre-TACE, the level of ALB decreased obviously after TACE in both groups ($P < 0.001$). In group A, it reached the valley at 1 week ($P < 0.001$) and rose obviously close to pre-TACE level at 4 weeks after TACE ($P < 0.05$). But in group B it decreased continuously and kept

TABLE 1 Characteristics of patients with HCC baseline(N=112)

Characteristic	Low-dose (n = 40)	Conventional- dose group (n = 42)	P value
Sex (M/F)	50/2	57/3	NS
Age (y)	48.5 ± 11.4	50.6 ± 12.3	NS
Tumber	8.29 ± 2.97	8.42 ± 2.76	NS
Number (single/multiple)	47/5	54/6	NS
Child-Pugh class (case)			
(A/B/C)	47/5/0	54/6/0	NS
Okuda stage(case)			
(I/II/III)	43/9/0	48/12/0	NS
Serum total bilirubin (μmol/l)	16.89 ± 7.38	17.78 ± 6.83	NS
Serum albumin (g/l)	36.95 ± 4.82	37.52 ± 3.87	NS
PV involvement (%)	48/4	55/5	NS
AFP (ng/L)	8/44	13/47	NS
(< 20 / > 20)			
Volume of the lipi- odol (ml)	11.6 ± 4.9	10.7 ± 5.5	NS
Embolic materials	36/16		
(PVA/GF)		40/20	NS
TACE times	2.05 ± 0.97	2.12 ± 0.76	NS

NS: no significant

under the pre-TACE level at 4 weeks after TACE ($P < 0.001$).

Seriously worsened hepatic function occurred in one case of group B after TACE. In clinic, jaundice and ascites aggravated with obvious increase of ALT level and Child-Pugh score from eight to eleven. Some complications, such as hepatic encephalopathy, hepato-renal syndrome and disturbance of acid-base balance occurred. Finally he died within 1 month after TACE. However, no patient with acute liver function failure occurred in group A.

Discussion

Transcatheter intra-arterial injection of lipiodol-anticancer drugs emulsion followed by gelfoam embolization is the most common method for treatment of HCC [1-10]. Lipiodol has the property of depositing selectively into tumor sinusoid, tissue interspace and small artery with a diameter of 25 ~ 150 μm. Anticancer drugs mixed with lipiodol may be stagnated in the tumor and released with a high concentration to strengthen its anticancer effect.

Under light and electron microscopies, most of the lipiodol-anticancer drugs emulsion can deposit granulously in the cytoplasm and even in nucleoli of tumor cells resulting in necrosis of tumors cells and normal liver cells around the tumor^[11,12]. Many clinical studies revealed that liver injury after TACE was an important factor to impose on long-term effect of patients, such as Farinati et al^[4] showed the survival rates of 1, 2 and 3 years in patients with Child A and B were 93%, 77% and 70% vs. 73%, 27% and 27% respectively. Mondazzi et al^[13] reported the survival rates of 12, 24 and 30 months in patients with Child A and B were 76%, 35% and 35% vs. 38%, 28% and 19% respectively. Moreover, HCC is frequently associated with the liver cirrhosis or other underlying liver diseases, therefore, using less anticancer drugs to protect liver function is the key to boost the survival rate of the patients after TACE.

To date, a controversy with the most suitable dosage of anticancer drugs is not resolved yet. Large dosage of anticancer drugs for TACE is constantly used in China, Korea and other Asian countries. In China, conventional dose of anticancer drugs is often used in TACE including MMC 10 ~ 30 mg, CDDP 60 ~ 120 mg, ADM 30 ~ 60 mg (or EPI 30 ~ 100 mg) and 5-FU 1000 ~ 1500 mg, combining 3 ~ 4 kinds of these drugs during once a procedure. Nevertheless, in western countries and Japan, a lower dosage is constantly used [3,4,14,15]. Recently, some authors have reported favorable results of TACE with low-dose anticancer drugs, such as Kamada et al^[3] reported a series patients of HCC using low-dose cisplatin in TACE obtained a satisfactory survival rate of 81%, 41%, 19% and 13% in 1, 3, 5 and 7 years respectively. Maeda et al^[16] reported TACE of HCC with low-dose cisplatin achieved the same effect as that of Kamada et al (survival rate 29.6% in 5 years). Berghammer et al^[17] even then suggested that single arterial embolization using permanent embolic agents without anticancer drugs was enough to prolong the survival rate of the patients with advanced HCC. The results of our previous study also showed that the therapeutic effect of TACE might be mainly attributed to the arterial embolization rather than the anticancer

Tab. 2 Changes of Child-Pugh Scores, serum TBIL, ALT and ALB after TACE in Low-dose and Conventional-dose Group

	Child-Pugh	TBIL($\mu\text{mol/L}$)	ALT($\mu\text{ kat/L}$)	ALB (g/l)	
Low-dose	Before TACE	5.8 ± 1.1	16.9 ± 7.4	0.96 ± 0.85	37.0 ± 4.8
	3d after TACE	7.0 ± 1.6 ^b	30.3 ± 19.3 ^b	3.43 ± 2.59 ^b	35.1 ± 5.2 ^b
	1w after TACE	6.2 ± 1.4 ^a	24.7 ± 15.2 ^b	1.97 ± 1.68 ^a	34.1 ± 4.5 ^b
	4w after TACE	6.2 ± 1.5	17.6 ± 9.9	1.00 ± 0.53	36.1 ± 4.8
Before TACE vs 3 d after TACE		<i>t</i> = 5.319	<i>t</i> = 6.707	<i>t</i> = 9.355	<i>t</i> = 2.704
Before TACE vs 1 w after TACE		<i>t</i> = 2.243	<i>t</i> = 4.774	<i>t</i> = 5.568	<i>t</i> = 7.120
Before TACE vs 4w after TACE		<i>t</i> = 1.890	<i>t</i> = 0.167	<i>t</i> = 0.396	<i>t</i> = 1.273
Conventional-dose	Before TACE	5.7 ± 1.0	17.8 ± 6.8	0.89 ± 0.57	37.5 ± 3.9
	3d after TACE	7.3 ± 1.6 ^b	42.1 ± 32.3 ^a	2.79 ± 2.11 ^b	34.8 ± 4.1 ^b
	1w after TACE	6.7 ± 1.2 ^b	37.7 ± 15.2 ^a	1.64 ± 0.78 ^b	33.2 ± 3.2 ^b
	4w after TACE	6.6 ± 1.4 ^b	27.6 ± 18.8 ^a	1.08 ± 0.65	33.5 ± 3.1 ^b
Before TACE vs 3 d after TACE		<i>t</i> = 8.859	<i>t</i> = 8.203	<i>t</i> = 9.820	<i>t</i> = 3.463
Before TACE vs 1 w after TACE		<i>t</i> = 4.645	<i>t</i> = 6.774	<i>t</i> = 8.747	<i>t</i> = 9.798
Before TACE vs 4 w after TACE		<i>t</i> = 2.630	<i>t</i> = 2.361	<i>t</i> = 1.596	<i>t</i> = 8.881

drugs^[18].

In addition to anti-cancer drugs and its dosage, the hepatic impairment after TACE could yet be related to the following factors, such as tumor stage, baseline liver function, embolic materials and methods, etc, and so a randomized controlled trial is necessary to assess the real impact of the anticancer drugs on liver function.

In this controlled study, there was no significant difference related to tumor stage, baseline liver functions, embolic materials and methods between the two groups (as seen in table 1). The results of this study revealed that TACE with low-dose anti-cancer drugs often induced transient impairment of liver function, on the contrary, in those patients using conventional dose of anti-cancer drugs the hepatic function impairment was usually serious and persistent after TACE. A significant statistical difference was present in the hepatic function impairment of both groups (as seen in table 2), with fully explaining of this mechanism.

[References]

- [1] Groupe d'Etude et de Traitement du Carcinome hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma[J]. N Eng J Med, 1995, 332: 1256 - 1261.
- [2] Pelletier G, Ducreux M, Gay F, et al. Treatment of unresectable hepatocellular: ation for unresectable hepatocellular carcinoma: comparison of cisplatin lipiodol suspension and doxorubicin hydrochloride emulsion[J]. JVIR, 2001, 12: 847 - 854.
- [3] Kamada K, Nakanishi T, Kitamoto M, et al. Long-term prognosis of patients undergoing transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: comparison of cisplatin lipiodol suspension and doxorubicin hydrochloride emulsion[J]. JVIR, 2001, 12: 847 - 854.
- [4] Farinati F, De Maria N, Marafin C, et al. Unresectable hepatocellular carcinoma in cirrhosis: survival, prognostic factor, and unexpected side effects after transcatheter arterial chemoembolization[J]. Dig Dis Sci, 1996, 41: 2332 - 2339.
- [5] Caturelli E, Siena DA, Villani MR, et al. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: evaluation of damage to nontumorous liver tissue-long-term prospective study[J]. Radiology, 2000, 215: 123 - 128.
- [6] Lin SC, Shih SC, Kao CR, et al. Transcatheter arterial embolization treatment in patients with hepatocellular carcinoma and risk of pulmonary metastasis [J]. World J Gastroenterol, 2003, 9: 1208 - 1211.
- [7] Fan J, Ten GJ, He SC, et al. Arterial chemoembolization for hepatocellular carcinoma[J]. World J Gastroenterol, 1998, 4: 33 - 37.
- [8] Chen MS, Li JQ, Zhang YQ, et al. High-dose iodized oil transcatheter arterial chemoembolization for patients with large hepatocellular carcinoma[J]. World J Gastroenterol, 2003, 9: 635 - 640.
- [9] Xiao EH, Li JQ, Huang JF. Effects of p53 on apoptosis and proliferation of hepatocellular carcinoma cells treated with transcatheter arterial chemoembolization [J]. World J Gastroenterol, 2004, 10: 190 - 194.

- [10] Guo WJ, Yu EX, Liu LM, et al. Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma [J]. World J Gastroenterol, 2003, 9: 1697 - 701.
- [11] Yamada R, Sato M, Nakatsuka H, et al. Hepatic artery embolization in 120 patients with unresectable hepatoma [J]. Radiology, 1983, 148: 397 - 401.
- [12] Sacheri S, Lovaria A, Sangiovanni A, et al. Segmental transcatheter arterial chemoembolization treatment in patients with cirrhosis and inoperable hepatocellular carcinomas [J]. J Vasc Interv Radiol, 2002, 13: 991 - 994.
- [13] Mondazzi L, Bottelli R, Brambilla G, et al. Transarterial oily chemoembolization for the treatment of hepatocellular carcinoma: a multivariate analysis of prognostic factors [J]. Hepatology, 1994, 19: 1115 - 23.
- [14] Yamasaki S, Hasegawa H, Kinoshita H, et al. A prospective randomized trial on the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma [J]. Jpn J Cancer Res, 1996, 87: 206 - 211.
- [15] Ikeda K, Kumada H, Saitoh S, et al. Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma [J]. Cancer, 1991, 68: 2150 - 2154.
- [16] Maeda S, Shibata J, Fujiyama S, et al. Long-term follow-up of hepatic: cisplatin suspended in iodized oil for hepatocellular carcinoma [J]. Hepato-gastroenterology, 2003, 50: 809 - 813.
- [17] Berghammer P, Pfeffel F, Winkelbauer F, et al. Arterial hepatic embolization of unresectable hepatocellular carcinoma using a cyanoacrylate/lipiodol mixture [J]. Cardiovasc Intervent Radiol, 1998, 21: 214 - 218.
- [18] Lu W, Li YH, He XF, et al. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: evaluation of two kinds of dosages of anticancer-drugs and analysis of prognostic factors [J]. Hepato-gastroenterology. 2003, 50: 2079 - 2083.

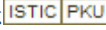
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《活体形态学》出版发行

由巫北海教授总主编的《活体形态学》05 年 5 月已由科学出版社出版,各地书店发行。该行是作者们总结了四十余年对活体形态学众多课题的研究成果、广泛收集国内外有关资料、以现代医学影像学技术为观察手段编写而成的。它全面、系统地介绍了活体各系统器官、组织(甚至细胞分子)的形态结构、功能状态及物质代谢变化情况。其特点是:活体、实时、无创或微创。而非活体形态学所见与之有较大差别。活体形态学可作为临床各科检查和观察病人的必备基础知识。该书共分颅脑、面颈、胸心、腹盆(上、下)和脊柱脊髓与肌骨系统六卷,是一套方便、实用的工具书。

Damage to Liver Function after TACE of Anticancer Drugs in Hepatocellular Carcinoma:Evaluation of Two Kinds of Anticancer Drugs

作者: LU Wei, LI Yan-hao, YU Zhi-jian, HE Xiao-feng, CHEN Yong, ZHAO Jian-bo
作者单位: 510515 Department of Interventional Radiology, Nanfang Hospital, Southern Medical University
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参考文献(18条)

1. [Groupe d'Etude et de Traitement du Carcinome hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma](#) 1995
2. [Pelletier G, Ducreux M, Gay F Treatment of unresectable hepatocellular:ation for unresectable hepatocellular carcinoma:comparison of cisplatin lipiodol suspension and doxorubicin hydrochloride emulsion](#) 2001
3. [Kamada K, Nakanishi T, Kitamoto M Long-term prognosis of patients undergoing transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma:comparison of cisplatin lipiodol suspension and doxorubicin hydrochloride emulsion](#) 2001
4. [Farinati F, De Maria N, Marafin C Unresectable hepatocellular carcinoma in cirrhosis:survival, prognostic factor, and unexpected side effects after transcatheter arterial chemoembolization](#) 1996
5. [Caturelli E, Siena DA, Villani MR Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis:evaluation of damage to nontumorous liver tissue-longterm prospective study](#) 2000
6. [Lin SC, Shih SC, Kao CR Transcatheter arterial embolization treatment in patients with hepatocellular carcinoma and risk of pulmonary metastasis](#)[期刊论文]-[World Journal of Gastroenterology](#) 2003(09)
7. [Fan J, Ten GJ, He SC Arterial chemoembolization for hepatocellular carcinoma](#)[期刊论文]-[World Journal of Gastroenterology](#) 1998(04)
8. [Chen MS, Li JQ, Zhang YQ High-dose iodized oil transcatheter arterial chemoembolization for patients with large hepatocellular carcinoma](#) 2003(09)
9. [Xiao EH, Li JQ, Huang JF Effects of p53 on apoptosis and proliferation of hepatocellular carcinoma cells treated with transcatheter arterial chemoembolization](#)[期刊论文]-[World Journal of Gastroenterology](#) 2004(10)
10. [Guo WJ, Yu EX, Liu LM Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma](#)[期刊论文]-[World Journal of Gastroenterology](#) 2003(09)
11. [Yamada R, Sato M, Nakatsuka H Hepatic artery embolization in 120 patients with unresectable hepatoma](#) 1983
12. [Sacheri S, Lovaria A, Sangiovanni A Segmental transcatheter arterial chemoembolization treatment in patients with cirrhosis and inoperable hepatocellular carcinomas](#) 2002
13. [Mondazzi L, Bottelli R, Brambilla G Transarterial oily chemoembolization for the treatment of hepatocellular carcinoma:a multivariate analysis of prognostic factors](#) 1994
14. [Yamasaki S, Hasegawa H, Kinoshita H A prospective ran-domized trial on the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma](#) 1996
15. [Ikeda K, Kumada H, Saitoh S Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma](#) 1991
16. [Maeda S, Shibata J, Fujiyama S Long-term follow-up of hepatic:cisplatin suspended in iodized oil for hepatocellular carcinoma](#) 2003
17. [Berghammer P, Pfeffel F, Winkelbauer F Arterial hepatic embolization of unresectable hepatocellular carcinoma using a cyanoacrylate/lipiodol mixture](#) 1998

18. [Lu W](#), [Li YH](#), [He XF](#) [Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis:evaluation of two kinds of dosages of anticancer-drugs and analysis of prognostic factors](#) 2003

引证文献(1条)

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