Hepatology Research

Hepatology Research 2015; **45**: 663–666 doi: 10.1111/hepr.12403

Original Article

Safety and efficacy of balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma

Hirotaka Arai,[1] Takehiko Abe,[1] Hisashi Takayama,[1] Mitsuo Toyoda,[1] Takashi Ueno,[1] Satoru Kakizaki[2] and Ken Sato[2]

[1]*Department of Gastroenterology, Maebashi Red Cross Hospital, and* [2]*Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Japan*

Aim: Balloon-occluded transcatheter arterial chemoembolization (B-TACE) using a microballoon catheter was performed to administrate miriplatin, and the early therapeutic efficacy and safety of the procedure were evaluated.

Methods: Out of 158 patients who received miriplatin using B-TACE for hepatocellular carcinoma, 49 patients with a single lesion at either stage I or II (according to the Liver Cancer Study Group of Japan) were evaluated in comparison with 48 matched patients who received miriplatin using conventional TACE (C-TACE).

Results: The mean total dose and median dose of miriplatin in each group were 32.5 ± 31.7 mg and 20 mg (C-TACE) and 50.1 ± 31.3 mg and 40 mg (B-TACE), respectively ($P < 0.01$). The treatment effect (TE) on the target nodule classified as TE4, TE3, TE2 or TE1 was 39.6%, 33.3%, 25.0% and 2.1%, respectively, in the C-TACE group, and 55.1%, 38.8%, 4.1% and 2.0%, respectively, in the B-TACE group. Therefore, the TE was significantly higher in the B-TACE group ($P < 0.05$). Although abdominal blood tests revealed adverse, increased levels of serum alanine aminotransferase (ALT) in a significantly higher number of B-TACE-treated patients, serum ALT levels returned to baseline levels in all patients within 1 month. There were no significant differences in clinical symptoms between the two groups.

Conclusion: Compared with C-TACE, B-TACE significantly improved cancer nodule control, and it was satisfactory in terms of safety. B-TACE is an effective procedure that enhances the effects of catheterization with miriplatin.

Keywords: balloon-occluded transcatheter arterial chemoembolization, hepatocellular carcinoma, miriplatin

INTRODUCTION

IN TRANSCATHETER ARTERIAL chemoembolization (TACE) for hepatocellular carcinoma (HCC), greater improvement of local control is achieved with better uptake of lipiodol (Lipiodol Ultrafluid; Terumo, Tokyo, Japan).[1] Balloon-occluded TACE (B-TACE), in which a microballoon catheter is used for TACE, is considered to improve the uptake of lipiodol into cancer nodules, as compared with conventional TACE (C-TACE).[2,3] Meanwhile, miriplatin (MIRIPLA; Dainippon Sumitomo Pharma, Osaka, Japan), which has high affinity for lipiodol, locally remains in tumors for a long period of time and thereby exerts prolonged antitumor effects but is minimally transferred to the systemic circulation. Based on these pharmacokinetic characteristics, miriplatin has recently been reported to be highly effective and safe.[4–6] In this study, we performed B-TACE to administrate miriplatin and evaluated the early therapeutic efficacy and safety of this procedure.

METHODS

A TOTAL OF 158 patients received miriplatin using B-TACE for HCC at our hospital between November 2011 and November 2013. Of these 158 patients, 49 with a single lesion at either stage I or II were included

Correspondence: Dr Hirotaka Arai, Department of Gastroenterology, Maebashi Red Cross Hospital, 3-21-36 Asahi-cho, Maebashi, Gunma 371-0014, Japan. Email: h-arai@maebashi.jrc.or.jp

Conflict of interest: The authors have no conflict of interests to disclose.

Financial sources: This study was supported by the authors' research funds.

Received 22 May 2014; revision 4 August 2014; accepted 5 August 2014.

Table 1 Patient and tumor characteristics

		B-TACE ($n = 49$)	C-TACE ($n = 48$)	
Age	Median (range)	71.9 (62–84)	69.9 (54–91)	n.s.
Sex	(M/F)	33/16	34/14	n.s.
Etiology	(HBV/HCV/NBNC)	1/41/7	4/36/8	n.s.
Child–Pugh grade	(A/B/C)	36/13/0	37/11/0	n.s.
Stage	(I/II/III)	16/33/0	22/26/0	n.s.
Tumor size (mm)	Median (range)	29 (8–73)	24.5 (14–90)	n.s.
Portal vein invasion		0	0	n.s.
Miriplatin dose (mg)	Median (range)	40 (10 120)	20 (5–120)	$P < 0.01$

B-TACE, balloon-occluded transcatheter arterial chemoembolization; C-TACE, conventional transcatheter arterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B, non-C; n.s., not significant.

in this study in comparison with 48 matched patients who received miriplatin using C-TACE (Table 1). All patients received information on the study and provided fully informed, written consent. The clinical study was approved by the hospital ethics committee and was performed in accordance with the internationally accepted ethical standards for human experimentation.

The indications for B-TACE were that the patients had no indications for hepatectomy/radiofrequency ablation. Each patient met the following criteria: a single cancer nodule was identified; the nodule was tumor stage I or II according to the staging system of the Liver Cancer Study Group of Japan;[7,8] there was no evidence of portal vein invasion; the patient had a Child–Pugh classification of A or B; adequate hematological function (white blood cell count ≥3000/μL, blood platelet count ≥50 000/μL, hemoglobin level ≥9.5 g/dL), adequate hepatic function (aspartate aminotransferase and alanine aminotransferase [ALT] levels ≤5-fold above maximum normal levels, serum bilirubin level <3 mg/dL, serum albumin level ≥3 g/dL), adequate renal function (serum creatinine ≤maximum normal levels); and an Eastern Cooperative Oncology Group performance status of 0–2 were recorded. B-TACE was performed according to the procedure reported by Irie *et al.*[2,3] Specifically, a microballoon catheter (Attendant [Terumo] or Logos [Piolax, Kanagawa, Japan]) was inserted into the tumor-feeding artery as peripherally as possible, and positioned in the subsegmental branch or segmental branch of the artery. The balloon was dilated to occlude the artery, and miriplatin was then administrated. It was injected until sufficient filling of the cancer nodule or overflow into the intrahepatic collateral pathway was observed. Subsequently, an embolic agent (Gelpart; Nihonkayaku, Tokyo, Japan) was injected into the blood vessel until a mold-like structure was formed, so long as permitted by the liver reserve capacity.

Conventional TACE was performed according to the following procedure. A microcatheter (Progreat; Terumo) was inserted into the tumor-feeding artery as peripherally as possible, and positioned in the subsegmental branch or segmental branch of the artery. Miriplatin was then administrated until the arterial blood flow reduced. Subsequently, an embolic agent was injected until the blood flow stopped.

The treatment effect (TE) on the target nodule was determined on computed tomography performed 1 month after treatment according to the Response Evaluation Criteria in Cancer of the Liver in the fifth supplementary edition of General Rules for the Clinical and Pathological Study of Primary Liver Cancer issued by the Liver Cancer Study Group of Japan.[9] The TE was defined as follows: TE4, disappearance or 100% necrosis of all treated tumors; TE3, more than 50% reduction in tumor size and/or more than 50% necrosis; and TE1, more than 25% increase in tumor size regardless of the necrotic effect. TE2 was defined as a response not qualifying for classification as TE4, TE3 or TE1. Safety was assessed according to the Japanese translation of the Common Terminology Criteria for Adverse Events version 4.0 by the Japan Clinical Oncology Group/Japan Society of Clinical Oncology.[10]

The Mann–Whitney *U*-test was used for comparisons between the two groups.

RESULTS

THE MEAN TOTAL dose and the median dose of miriplatin were 32.5 ± 31.7 mg and 20 mg, respectively, in the C-TACE group, and 50.1 ± 31.3 mg and

Table 2 Treatment effect of TACE using miriplatin

	B-TACE ($n = 49$), n	C-TACE ($n = 48$), n
TE4	27 (55.1%)	19 (39.6%)
TE3	19 (38.8%)	16 (33.3%)
TE2	2 (4.1%)	12 (25.0%)
TE1	1 (2.0%)	1 (2.1%)

$P < 0.05$. B-TACE, balloon-occluded transcatheter arterial chemoembolization; C-TACE, conventional transcatheter arterial chemoembolization; TE, treatment effect.

40 mg respectively, in the B-TACE group. The mean total dose was significantly higher in the B-TACE group ($P < 0.01$) (Table 1). The TE, classified as TE4, TE3, TE2 or TE1, were 39.6%, 33.3%, 25.0% and 2.1% in the C-TACE group; and 55.1%, 38.8%, 4.1% and 2.0% in the B-TACE group, respectively. Significantly higher TE values were observed in the B-TACE treatment group ($P < 0.05$) (Table 2).

The adverse effects observed after TACE using miriplatin are shown in Table 3. There were no significant differences in the clinical symptoms between the two groups. Moreover, no clinical symptoms of grade 3 or higher severity were observed in either group. Serum ALT levels increased after the TACE procedures in most of the patients, and grade 3 elevation was found in four patients (8.3%) in the C-TACE group and seven patients (14.3%) in the B-TACE group. The increase in serum ALT was significantly higher in the B-TACE group ($P < 0.05$). The serum ALT levels returned to the baseline levels in all patients within 1 month.

DISCUSSION

IN ACTUAL CLINICAL practice, when catheterization with miriplatin is performed, there are many cases in which the tumor-feeding artery becomes occluded before a sufficient amount of the drug reaches cancer nodules. Thus, in an effort to enhance therapeutic effects, we administrated miriplatin and an embolic agent under balloon occlusion.

The therapeutic effects of B-TACE were significantly higher than those of C-TACE, and improved drug uptake into cancer nodules was observed. With the conventional procedure, because drugs are forced into lesions by arterial blood pressure, they flow into both the cancer nodules and the portal system. However, because intravascular pressure is decreased under balloon occlusion, drugs are considered to not flow into the portal vein but

Table 3 Adverse events observed after TACE using miriplatin

	B-TACE ($n = 49$), n				C-TACE ($n = 48$), n				
	Grade				Grade				
	1	2	3	4	1	2	3	4	
Nausea, vomiting	8 (16.3%)	0 (0%)	0 (0%)	0 (0%)	5 (10.4%)	0 (0%)	0 (0%)	0 (0%)	n.s.
Fever	22 (44.9%)	5 (10.2%)	0 (0%)	0 (0%)	19 (39.6%)	1 (2.0%)	0 (0%)	0 (0%)	n.s.
Abdominal pain	18 (36.7%)	0 (0%)	0 (0%)	0 (0%)	12 (25.0%)	1 (2.0%)	0 (0%)	0 (0%)	n.s.
Ascites	6 (12.2%)	0 (0%)	0 (0%)	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)	0 (0%)	n.s.
Elevation of total bilirubin	15 (30.6%)	10 (20.4%)	0 (0%)	0 (0%)	17 (35.4%)	6 (12.5%)	0 (0%)	0 (0%)	n.s.
Elevation of ALT	27 (55.1%)	12 (24.5%)	7 (14.3%)	0 (0%)	30 (62.5%)	7 (14.6%)	4 (8.3%)	0 (0%)	$P < 0.05$
Elevation of serum creatinine	3 (6.1%)	1 (2.0%)	0 (0%)	0 (0%)	5 (10.4%)	0 (0%)	0 (0%)	0 (0%)	n.s.
Leukocytopenia	17 (34.7%)	9 (18.4%)	0 (0%)	0 (0%)	13 (27.1%)	13 (27.1%)	1 (2.1%)	0 (0%)	n.s.
Thrombocytopenia	25 (51.0%)	12 (24.5%)	6 (12.2%)	0 (0%)	21 (43.8%)	15 (31.3%)	6 (12.5%)	0 (0%)	n.s.

ALT, alanine aminotransferase; B-TACE, balloon-occluded transcatheter arterial chemoembolization; C-TACE, conventional transcatheter arterial chemoembolization; n.s., not significant.

rather to flow preferentially into cancer nodules.[2,3] The results of this study confirmed B-TACE using miriplatin to exert similar effects, suggesting that early occlusion of the tumor-feeding artery/backflow of drugs was prevented by employing this procedure.

The reasons for the significantly higher total dose of miriplatin in the B-TACE group seemed to be that the dose was increased as a consequence of improved uptake of miriplatin into cancer nodules due to the effects of balloon occlusion.

With regard to any adverse events, significantly more patients in the B-TACE group had increased levels of serum ALT than in the C-TACE group. However, ALT levels returned to the baseline levels in all patients within 1 month. There were no significant differences in the clinical symptoms observed between the two groups. It was assumed that B-TACE can be performed as safely as C-TACE. Miriplatin is considered to cause fewer systemic adverse reactions because it locally remains in tumors for a long period of time but is minimally transferred to the systemic circulation.[4–6] Thus, apparently, even if local drug uptake is enhanced by B-TACE, there may be a small systemic effect.

Further accumulation of clinical experience and future studies are necessary to assess the long-term efficacy and safety of B-TACE.

In conclusion, compared with C-TACE, B-TACE significantly improved cancer nodule control, and it was satisfactory in terms of safety. B-TACE is an effective procedure that enhances the effects of catheterization with miriplatin.

REFERENCES

1 Miyayama S, Matsui O, Yamashiro M *et al*. Ultraselective transcatheter arterial chemoembolization with a 2-f tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. *J Vasc Interv Radiol* 2007; **18:** 365–76.
2 Irie T, Kuramochi M, Takahashi N. Dense accumulation of lipiodol emulsion in hepatocellular carcinoma nodule during selective balloon-occluded transarterial chemoembolization: measurement of balloon-occluded arterial stump pressure. *Cardiovasc Intervent Radiol* 2013; **36:** 706–13.
3 Irie T, Kuramochi M, Takahashi N. Improved accumulation of lipiodol under balloon-occluded transarterial chemoembolization (B-TACE) for hepatocellular carcinoma: measurement of blood pressure at the embolized artery before and after balloon inflation. *Jpn J Intervent Radiol* 2011; **26:** 49–54. (In Japanese.)
4 Okusaka T, Okada S, Nakanishi T *et al*. Phase?trial of intra-arterial chemotherapy using a novel lipophilic platinum derivative (SM-11355) in patients with hepatocellular carcinoma. *Invest New Drugs* 2004; **22:** 169–76.
5 Imai N, Ikeda K, Kawamura Y *et al*. Transcatheter arterial chemotherapy using miriplatin-lipiodol suspension with or without embolization for unresectable hepatocellular carcinoma. *Jpn J Clin Oncol* 2012; **42:** 175–82.
6 Okabe K, Beppu T, Haraoka K *et al*. Safety and short-term therapeutic effects of miriplatin-lipiodol suspension in transarterial chemoembolization (TACE) for hepatocellular carcinoma. *Anticancer Res* 2011; **31:** 2983–8.
7 The Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan. Report 13. *Kanzo* 1999; **40:** 288–300.
8 The Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan. Report 14. *Kanzo* 2000; **41:** 799–811.
9 The Liver Cancer Study Group of Japan. The fifth supplementary edition of General Rules for the Clinical and Pathological Study of Primary Liver Cancer. 2009.
10 The Japan Clinical Oncology Group (JCOG)/Japan Society of Clinical Oncology (JSCO). The Japanese translation of the Common Terminology Criteria for Adverse Events version 4.0. 2010.