

Feasibility and Safety of Repeated Transarterial Chemoembolization Using Miriplatin–Lipiodol Suspension for Hepatocellular Carcinoma

TOMOHIRO MATSUMOTO^{1*}, HITOSHI ICHIKAWA², JIN IMAI², TOSHIHIKO HAYASHI¹, KOSUKE TOMITA¹, TAKAHIKO MINE¹, SEIICHIRO KOJIMA², NORIHITO WATANABE² and TERUMITSU HASEBE^{1*}

Departments of ¹Radiology and ²Gastroenterology, Tokai University Hachioji Hospital, Tokai University School of Medicine, Hachioji, Japan

Abstract. *Aim: To retrospectively evaluate the feasibility and safety of repeated transarterial chemoembolization (TACE) three or more times using miriplatin-lipiodol (M-LPD) suspension (repeated M-LPD TACE) for hepatocellular carcinoma (HCC). Patients and Methods: Sixteen patients who underwent repeated M-LPD TACE were examined. Total dose of miriplatin, lipiodol and porous gelatin sponge particles and adverse events of the first and last M-LPD TACE were evaluated. Results: The mean±standard deviation (SD) of the total number of M-LPD TACE per patient was 3.7±1.1. The mean±SD dose of total miriplatin, lipiodol and porous gelatin sponge particles per patient was 303±103 mg, 21±7.3 ml and 84±57 mg, respectively. There were no significant differences in any adverse events between the first and last M-LPD TACE. Conclusion: Repeated M-LPD TACE for HCC is feasible and safe in selected patients.*

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases worldwide (1). Transarterial chemoembolization (TACE) is the most frequently used treatment for managing unresectable HCC, with proven improvement in survival of selected patients (2, 3). The first platinum-based anticancer agent, cisplatin, has remarkable antitumor effects in TACE (4-7). However, cisplatin is rather hydrophilic and

barely soluble in lipiodol (Andre Guerbet, Aulnay-sous-Bois, France), which is a carrier of anticancer agents for targeted chemotherapy for HCC, even when prepared as a powder to increase its solubility in lipiodol. Therefore, only a small volume of cisplatin remains in the tumor for a long period, and most of the agent is released briefly into the bloodstream in the systemic circulation and cause systemic side-effects such as nausea/vomiting and renal dysfunction (8). Furthermore, it has also been reported that hypersensitivity reactions as an adverse effect occurred in 8.9% of patients who underwent three or more TACE sessions using cisplatin–lipiodol suspension (C-LPD) (9). Recently, a new platinum-based anticancer agent, miriplatin (Dainippon Sumitomo Pharma Co., Ltd, Osaka, Japan), that is easily suspended in lipiodol, was developed for intra-arterial treatment of HCC in Japan (10). When lipiodol is injected into an artery supplying HCC nodules, it selectively accumulates in the tumor. A miriplatin–lipiodol suspension (M-LPD) deposited within HCC nodules will gradually release active platinum compounds into tumor tissues, thereby exerting prolonged antitumor effects; however, it is minimally transferred into the systemic circulation. Based on these pharmacokinetic characteristics, conventional TACE using M-LPD, performed using M-LPD followed by porous gelatin sponge particles, and transarterial infusion chemotherapy using M-LPD have recently been reported to be highly effective and safe (8, 11-13). Additionally, M-LPD has been safely used as an anticancer drug in balloon-occluded TACE (14), which has the potential to improve cancer nodule control locally, compared with conventional TACE (15, 16). However, the feasibility and safety of repeated M-LPD TACE three or more times including conventional and balloon-occluded TACE (repeated M-LPD TACE) has not yet been evaluated because previous reports on M-LPD TACE dealt with single session only.

Therefore, the purpose of this study was to retrospectively evaluate the feasibility and safety of repeated M-LPD TACE for HCC.

*These Authors contributed equally to this study.

Correspondence to: Professor Terumitsu Hasebe, MD, Ph.D. (Dr. Eng.), Professor and Chairman, Department of Radiology, Tokai University Hachioji Hospital, Tokai University School of Medicine, 1838 Ishikawa-machi, Hachioji, Tokyo 192-0032, Japan. Tel: +81 426391111, Fax: +81 426391144, e-mail: hasebe@tokai-u.jp

Key Words: Transarterial chemoembolization, hepatocellular carcinoma, miriplatin.

Patients and Methods

Study design. This retrospective study was conducted with the approval of the Institutional Review Board (16R-263). Informed consent was obtained for every diagnostic and interventional procedure.

Patients. Between January 2013 and December 2016, 61 patients received repeated M-LPD TACE for the treatment of HCC at our Institution. The inclusion criteria for this study were as follows: (a) the first M-LPD TACE for HCC was initial TACE and (b) only miriplatin was used as the anticancer drug in TACE (Figure 1). Finally, 16 out of the 61 patients (26%) were included in the study. There were 10 males and six females, with a mean age±standard deviation (SD) of 73±7 years (range=58-83 years) (Table I).

The diagnosis of HCC was made based on distinctive computed tomography (CT) and magnetic resonance imaging (MRI) findings, in addition to high serum levels of tumor markers [α -fetoprotein (AFP) or protein induced by vitamin K absence or antagonist-II (PIVKA-II)] (Table I).

TACE. All TACE procedures were performed by three interventional radiologists (T. H., T. M. and T.M.) with more than 10 years' experience in hepatic vascular interventions, using the same angiographic flat-panel detector system (Siemens Medical Solutions, Forchheim, Germany). An appropriate microcatheter or microballoon catheter was coaxially inserted through a 4-Fr catheter via the femoral artery and placed into the tumor feeder vessel. After tumor location was confirmed, infusion of M-LPD, which was prepared by dissolving 70 mg of miriplatin in 4 or 5 ml of lipiodol warmed to 40°C, was initiated, followed by embolization of each hepatic area containing the target tumors with porous gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan) 1 or 2 mm in diameter. When TACE using a microballoon catheter was performed, M-LPD infusion was continued under microballoon occlusion. Details of microballoon catheter characteristics are summarized elsewhere (14, 17). The end-point of M-LPD infusion in conventional and balloon-occluded TACE was as follows: the HCC nodule filled with M-LPD or the portal venous branches were beginning to be filled with M-LPD. The dose of miriplatin and lipiodol per session was limited to 140 mg and 10 ml for all patients, respectively.

Parameters investigated. We investigated total dose of M-LPD and porous gelatin sponge particles, and adverse events of the first and last M-LPD TACE, which were graded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) (18).

Statistical analysis. For statistical analysis, commercial software (JMP 12; SAS Japan, Tokyo, Japan) was used. Statistical analyses were performed using the Wilcoxon test or Wilcoxon signed-rank test for nonparametric data as appropriate. Differences were considered significant when the *p*-value was 0.05 or in the analyses.

Results

The total number of M-LPD TACE was 59 sessions. The total number of repeated M-LPD TACE was 27 sessions. The mean±SD number of M-LPD TACE per patient was 3.7±1.1

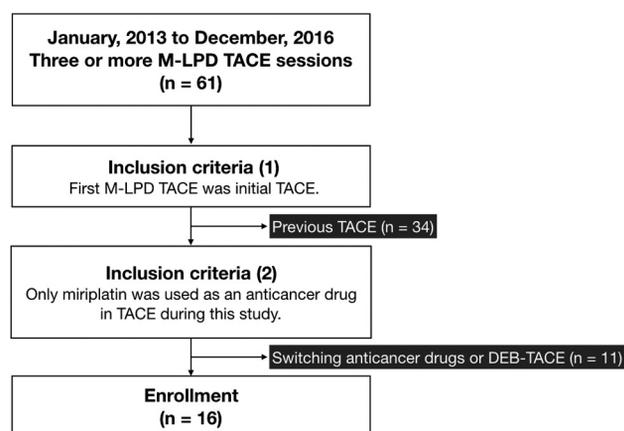


Figure 1. Flowchart for the patients of this study. M-LPD: Miriplatin-lipiodol suspension, TACE: Transarterial chemoembolization, DEB-TACE: TACE with drug-eluting beads.

Table I. Patient characteristics of this study (n=16).

| | |
|---------------------------------|---------------------|
| Mean age±SD (range), years | 73±7 (58-83) |
| Gender, n | |
| Male | 10 |
| Female | 6 |
| Etiology, n | |
| HCV | 8 |
| Other | 8 |
| Median AFP (range), ng/ml | 28.25 (3.4-55234.7) |
| Median PIVKA-II (range), mAU/ml | 107.5 (10-3735) |
| Stage* | |
| I | 2 |
| II | 12 |
| III | 2 |
| IV | 0 |

SD: Standard deviation, HCV: hepatitis C virus, AFP: α -fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonists-II. *Staging as proposed by the Liver Cancer Study Group of Japan.

(range=3-7) sessions. M-LPD TACE was performed at intervals of 231±189 (42-836) days.

The mean±SD dose of miriplatin, lipiodol and porous gelatin sponge particles per patient was 303±103 (range=182-492.8) mg, 21±7.3 (range=13-35) ml and 84±57 (range=28-246.4) mg, respectively. The mean±SD dose of miriplatin, lipiodol and porous gelatin sponge particles per session was 83±36 (range=21-140) mg, 5.9±2.6 (range=1.5-10) ml and 22±21 (range=4-44) mg, respectively.

There were no significant differences in Child-Pugh score before the procedure and dose of miriplatin, lipiodol and porous gelatin sponge particles between the first and last M-LPD TACE groups (Table II).

Table II. Characteristics of the first and last miriplatin-lipiodol suspension transarterial chemoembolization (M-LPD TACE) (n=16). Data are the mean±SD (range).

| | First M-LPD TACE | Last M-LPD TACE | p-Value |
|---------------------------------------|------------------|-------------------|---------|
| Child-Pugh score before the procedure | 5.75±0.8 (5-7) | 5.75±1.1 (5-8) | 1.0000* |
| Miriplatin (mg) | 77±38 (33.6-140) | 91±39 (28-140) | 0.2978# |
| LPD (ml) | 5.2±2.8 (2-10) | 6.6±2.6 (2-10) | 0.1505# |
| Porous gelatin sponge particle (mg) | 22±21 (4-64) | 24±11 (11.2-54.4) | 0.122# |

*Wilcoxon signed-rank, #Wilcoxon test.

Fever, anorexia and elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were observed in most patients after the procedure in both the first and last M-LPD TACE groups. Grade 4 AST elevations were seen in one patient (6%) in both the first and last M-LPD TACE groups. Grades 1 and 2 serum creatinine elevation in the first M-LPD TACE group were observed in one (6%) and two patients (13%), respectively. Grades 1 and 2 serum creatinine elevation in the last M-LPD TACE group were observed in two (13%) and one patient (6%), respectively. The three patients in whom serum creatinine elevation was observed after the first and last M-LPD TACE were the same (Table III). The patients' creatinine levels before the first and last M-LPD TACE was the upper limit of normal or slightly high (Table III). Elevation of the serum creatinine level up to 2.32 mg/dl was observed after the last M-LPD TACE in one patient (Table III). However, recovery from the adverse effect took place within one week. No other serious complications such as liver abscess, hypersensitivity reaction to miriplatin or treatment-related deaths were observed in any M-LPD TACE session.

There were no significant differences between the first and last M-LPD TACE groups in terms of any adverse events (Table IV).

Discussion

According to Fujiyama *et al.*, the pharmacokinetic parameters of miriplatin, namely C_{max} (maximum drug concentration), T_{max} (time to maximum drug concentration) and $t_{1/2}$ (half-life) are 5.3-14.2 mg/ml, 7-183 days and 18.4-707.2 days, respectively (19), in comparison with those of cisplatin for which C_{max} is 2-3 µg/ml and $t_{1/2}$ is 5-7 days (4), are considerably lower; C_{max} and T_{max} of miriplatin are each approximately 1/100-1/500 than that of cisplatin, but the half-life is much longer. This reflects the sustained release properties of M-LPD. On the other hand, there is a potential risk for an increase in some adverse events such as hematological toxicity, nausea/vomiting, hypersensitivity reactions and renal dysfunction by repeated M-LPD TACE, paralleling increasing residual miriplatin in the body by

Table III. The course of creatinine (Cr) level in patients with Cr increase.

| Patient no. | Cr level (mg/dl) | | | |
|-------------|------------------|-------|-----------------|-------|
| | First M-LPD TACE | | Last-M-LPD TACE | |
| | Before | After | Before | After |
| 1 | 1.43 | 1.73 | 1.48 | 2.32 |
| 2 | 1.08 | 1.14 | 1.09 | 1.13 |
| 3 | 1.65 | 1.79 | 1.92 | 1.59 |

M-LPD TACE: Miriplatin-lipiodol suspension transarterial chemoembolization.

performing repeated M-LPD TACE. However, there have been no reports on relevant clinical investigations.

In our study, the toxicity profile for repeated M-LPD TACE was mild and acceptable. There were no significant differences in the Child-Pugh score before the procedure and dose of miriplatin, lipiodol and porous gelatin sponge particles between the first and last M-LPD TACE groups. Furthermore, there were no significant differences in any adverse events between the first and last M-LPD TACE groups. These results suggest that residual miriplatin after performing repeated M-LPD TACE had little or no impact on the patients of our study.

Anorexia and fever frequently emerged as adverse effects in both the first and last M-LPD TACE groups. However, these are reactions that usually accompany hepatic intra-arterial infusion as a therapeutic modality. Elevations of serum AST and ALT were observed quite frequently in both the first and last M-LPD TACE groups.

Transient elevations of serum transaminase levels are commonly observed following conventional TACE using M-LPD (8, 11-13), balloon-occluded TACE using M-LPD (14) and TACE using other anticancer agents (7, 20-22).

Renal dysfunction is a typical problem with C-LPD TACE. However, repeated M-LPD TACE were possible even in cases of slight renal function decline in our study.

Table IV. Adverse effects after first and last transarterial chemoembolization with miriplatin-lipiodol suspension (M-LPD TACE) (n=16).

| Adverse effect | First M-LPD TACE, n (%) | | | | | Last M-LPD TACE, n (%) | | | | | p-Value* |
|-------------------------------------|-------------------------|--------------------|---------|---------|--------|------------------------|--------------------|---------|---------|--------|----------|
| | Total | Grade (CTCAE v4.0) | | | | Total | Grade (CTCAE v4.0) | | | | |
| | | 1 | 2 | 3 | 4 | | 1 | 2 | 3 | 4 | |
| White blood cell decrease | 5 (31%) | 2 (13%) | 2 (13%) | 1 (6%) | 0 (0%) | 5 (31%) | 1 (6%) | 2 (13%) | 2 (13%) | 0 (0%) | 0.7813 |
| Aspartate aminotransferase increase | 16 (100%) | 6 (38%) | 2 (13%) | 7 (44%) | 1 (6%) | 16 (100%) | 4 (25%) | 4 (25%) | 7 (44%) | 1 (6%) | 0.8066 |
| Alanine aminotransferase increase | 14 (88%) | 5 (31%) | 2 (13%) | 7 (44%) | 0 (0%) | 13 (81%) | 3 (19%) | 3 (19%) | 7 (44%) | 0 (0%) | 0.9805 |
| Total bilirubin increase | 11 (69%) | 7 (44%) | 4 (25%) | 0 (0%) | 0 (0%) | 12 (75%) | 9 (56%) | 2 (13%) | 1 (6%) | 0 (0%) | 1.0000 |
| Creatinine increase | 3 (19%) | 1 (6%) | 2 (13%) | 0 (0%) | 0 (0%) | 3 (19%) | 2 (13%) | 1 (6%) | 0 (0%) | 0 (0%) | 1.0000 |
| Nausea/vomiting | 2 (13%) | 2 (13%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (13%) | 2 (13%) | 0 (0%) | 0 (0%) | 0 (0%) | 1.0000 |
| Fever | 9 (56%) | 8 (50%) | 1 (6%) | 0 (0%) | 0 (0%) | 11 (69%) | 10 (63%) | 1 (6%) | 0 (0%) | 0 (0%) | 1.0000 |
| Abdominal pain | 6 (38%) | 4 (25%) | 0 (0%) | 2 (13%) | 0 (0%) | 5 (31%) | 3 (19%) | 2 (13%) | 0 (0%) | 0 (0%) | 0.7188 |
| Anorexia | 12 (75%) | 12 (75%) | 0 (0%) | 0 (0%) | 0 (0%) | 14 (83%) | 13 (81%) | 0 (0%) | 1 (6%) | 0 (0%) | 0.5000 |

CTCAE v4.0: Common Terminology Criteria for Adverse Events version 4.0 (18). *Wilcoxon signed-rank test.

No hypersensitivity reactions as an adverse effect occurred in any M-LPD TACE session. Although the mechanism of cisplatin-induced hypersensitivity remains unknown, hypersensitivity reactions to platinum compounds seem to be generally mediated by type I hypersensitivity, and platinum compounds dependently induce the direct release of histamine as another mechanism of the hypersensitivity (23). In particular, patients who received three or more sessions of C-LPD conventional TACE had a 13-fold increase in the risk of hypersensitivity reactions (9). Indeed, differences between M-LPD and C-LPD TACE in respect of hypersensitivity reactions as adverse effects are unclear. However, repeated M-LPD TACE may be desirable from the viewpoint of minimizing hypersensitivity reactions.

There are some limitations to the present study, the first being its retrospective design. Secondly, this study was limited by its small sample size. Lastly, we did not evaluate the changes in platinum concentration in the plasma. However, to the best of our knowledge, the present study is the first work that shows the feasibility and safety of repeated M-LPD TACE. Therefore, further investigations into the safety and therapeutic efficacy of repeated M-LPD TACE are clearly necessary.

In conclusion, repeated M-LPD TACE for HCC is feasible and safe in selected patients.

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Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest in regard to this study.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. None of the Authors was involved in any studies with animals in relation to the preparation of this article.

Informed Consent

Informed consent was obtained from all participants included in the study.

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