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Microwave ablation combined with transarterial chemoembolization containing doxorubicin hydrochloride liposome for treating primary and metastatic liver cancers

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ABSTRACT

Aims: To determine the safety and efficacy of microwave ablation (MWA) and transarterial chemoembolization (TACE) with doxorubicin hydrochloride liposome (DHL) in patients with primary liver cancer (PLC) and metastatic liver cancer (MLC).

Materials and methods: The medical records of patients with primary or metastatic liver cancer who underwent MWA combined with TACE containing DHL from March 2019 to March 2022 were collected and analyzed. Treatment-related adverse events (AEs) were recorded. Local tumor response was evaluated according to the modified RECIST criteria. Local tumor progression-free survival (LTPFS) and overall survival (OS) were calculated using the Kaplan-Meier method.

Results: Altogether, 96 patients with liver cancer were included (PLC, n = 45; MLC, n = 51). Forty (41.7%) patients experienced AEs during treatment, and eight (8.3%) patients developed grade 3 AEs. Compared to before treatment, the serum total bilirubin level and neutrophil to lymphocyte ratio significantly increased after treatment. The median LTPFS was 14.5 months in patients with PLC and 10.7 months in patients with MLC. The median OS was not reached in patients with PLC or MLC. The 1-month and 3-month disease control rates reached more than 80% in both groups.

Conclusion: MWA combined with TACE with DHL may be a safe and effective method for the treatment of liver cancer.

1. Introduction

Transarterial chemoembolization (TACE) is one of the most popular treatment methods in patients with unresectable primary liver cancer (PLC) or metastatic liver cancer (MLC).[1–3] The rationale is that chemotherapeutic drugs and embolic agents are delivered into tumor-feeding blood vessels to induce strong ischemic and cytotoxic effects targeting the tumor. However, some studies have demonstrated that the tumor response and survival rates were statistically similar between TACE and transarterial embolization.[4,5] This may be because traditional small-molecule drugs are not ideal for combination with embolization. Moreover, these drugs have a relatively high systemic toxicity. In recent years, nanodrugs have been used to treat solid tumors in clinical practice because of their low toxicity, high targeting and slow release.[6–8] Doxorubicin hydrochloride liposomes (DHL) are common liposome preparations that encapsulate doxorubicin hydrochloride in liposomes containing methoxy polyethylene glycol on their surface.[9] This can prolong drug circulation in the blood with less systemic toxicity.

Microwave ablation (MWA) has some advantages when combined with TACE in some patients with PLC or MLC. Previous studies have demonstrated that combination therapy could provide better tumor control and survival benefit over TACE alone.[10,11] MWA can directly

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destroy some relatively hypovascular liver tumors that do not respond well to TACE alone.[12] TACE can complement the treatment of residual tumors by the occlusion of tumor-feeding arteries and the cytotoxic effect of drugs. A preclinical study has reported that a doxorubicin-loaded liposome could be an efficient nanoplatform for enhancing the efficacy of MWA in the treatment of hepatocellular carcinoma.[13] In this study, we determined the safety and efficacy of MWA combined with TACE containing DHL in patients with primary and metastatic liver cancer.

2. Materials and methods

2.1. Study design and patient selection

In this single-center retrospective study, we collected and analyzed the electronic medical records of patients with PLC or MLC who underwent MWA and TACE with DHL between March 2019 and March 2022. The eligibility criteria mainly included primary or metastatic liver cancer confirmed based on histology or a typical imaging profile with dynamic CT or MRI. Other inclusion criteria were Child-Pugh class A or B, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, 18 years or older and underwent at least one MWA combined with TACE containing DHL in our institution. Patients were excluded if they had incomplete medical records, underwent TACE containing DHL as the initial treatment, participated in other clinical trials, or had serious comorbidities, including hepatic encephalopathy, refractory ascites, and esophageal variceal bleeding. This study was approved by the institutional review board and complied with the Declaration of Helsinki and applicable local laws. Written informed consent was obtained from all patients.

2.2. MWA and TACE procedure

MWA and synchronous TACE were performed in the study. First, the femoral artery (or radial artery) route was percutaneously punctured for cannulation using the Seldinger technique. Catheterization of the celiac trunk or common hepatic artery for digital subtraction angiography (DSA) was performed to identify tumor-feeding arteries, tumor number, and location. Then, a water-cooled microwave system (VISON-CHINA MEDICAL DEVICES R&D CENTER, USA) was used to perform MWA under ultrasound imaging. The placement of the antennae, power output setting, and ablation time were determined based on the tumor size, number and distance from vulnerable structures (liver capsule, clearly visible bile duct or blood vessels). During the ablation procedure, 10 mg DHL (Jinyuan Pharmaceutical Manufacturing Co., LTD, Changzhou, China) was infused via the hepatic artery. Subsequently, the needle track was coagulated to prevent bleeding or tumor seeding. Arteriography was performed again to evaluate the tumor staining and ablative results. Superselective catheterization of residual tumor-feeding arteries was performed for TACE treatment. The emulsion of chemotherapeutic agents (10 mg DHL with or without 2 mg raltitrexed, 100 mg irinotecan or 50 mg oxaliplatin) and 5–10 mL lipiodol were delivered into the targeted arteries to achieve ultraterminal embolization. Subsequently, embolization with blank microspheres or gelatin sponge particles was performed until arterial flow stasis under X-ray. The endpoint of embolization was confirmed using postoperative angiography.

2.3. Outcomes

Effectiveness was evaluated in terms of overall survival (OS), local tumor progression-free survival (LTPFS) and local tumor response. LTPFS was defined as the period from the local treatment to local radiological progression or death.[14] Local tumor response included 1-month and 3-month objective response rates (patients with complete or partial response) as well as disease control rates (patients with complete response, partial response or stable disease maintained for ≥4 weeks), assessed by investigators using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.[15] Patients were followed up until death, the last follow-up, or the end of the study (06–2022).

All patients were regularly followed up after the treatment. Each follow-up period included laboratory tests, clinical examinations and imaging evaluations. Patients with residual viable or intrahepatic recurrent tumors on contrast-enhanced CT or MRI would receive a second treatment if their condition permitted. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Chicago, USA) and GraphPad Prism version 8.0 (GraphPad Prism, San Diego, USA). The continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. The Wilcoxon signed-rank test was used to determine the differences in laboratory tests before and after treatment. Survival curves were calculated using the Kaplan-Meier method. Data with a P value less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The detailed baseline characteristics of all patients are shown in Table 1. A total of 96 patients with PLC (n = 45) or MLC (n = 51) were included with a mean age of 56.4 ± 12.8 years old, of which 67 (69.8%) were male. Most patients had more than 3 lesions (n = 55, 57.3%) and were mainly in the MLC group (n = 39, 76.5%). The mean maximal tumor diameter was 4.2 ± 3.1 cm, with 28 (29.2%) patients having a

Table 1
Baseline patient characteristics.

Characteristic	Total (n = 96)	PLC (n = 45)	MLC (n = 51)
Age (y)	56.4 ± 12.8	57.0 ± 12.0	55.9 ± 13.5
Sex			
Male	67 (69.8)	36 (80.0)	31 (60.8)
Female	29 (30.2)	9 (20.0)	20 (39.2)
Tumor location			
Unilobar	41 (42.7)	23 (51.1)	18 (35.3)
Bilobar	55 (57.3)	22 (48.9)	33 (64.7)
ECOG PS			
0	71 (74.0)	39 (86.7)	32 (62.7)
1	25 (26.0)	6 (13.3)	19 (37.3)
Child-Pugh class			
A	92 (95.8)	44 (97.8)	48 (94.1)
B	4 (4.2)	1 (2.2)	3 (5.9)
ALBI grade			
1	79 (82.3)	35 (77.8)	44 (86.3)
2	17 (17.7)	10 (22.2)	7 (13.7)
Maximal tumor diameter			
Mean ± SD (cm)	4.2 ± 3.1	4.8 ± 3.8	3.7 ± 2.2
< 5 cm	68 (70.8)	28 (62.2)	40 (78.4)
≥ 5 cm	28 (29.2)	17 (37.8)	11 (21.6)
No. of tumors			
≤3	41 (42.7)	29 (64.4)	12 (23.5)
> 3	55 (57.3)	16 (35.6)	39 (76.5)
Vascular invasion	12 (12.5)	9 (20.0)	3 (5.9)
Extrahepatic spread	13 (13.5)	6 (13.3)	7 (13.7)
Chemotherapy agents			
DHL alone	32 (33.3)	22 (48.9)	10 (19.6)
Combined raltitrexed	30 (31.3)	13 (28.9)	17 (33.3)
Combined irinotecan	27 (28.1)	7 (15.6)	20 (39.2)
Combined oxaliplatin	7 (7.3)	3 (6.7)	4 (7.8)

Abbreviations: PLC, primary liver cancer; MLC, metastatic liver cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ALBI, albumin-bilirubin; SD, standard deviation; DHL, doxorubicin hydrochloride liposome; MWA-TACE, microwave ablation combined with transarterial chemoembolization.

tumor diameter of larger than 5 cm. Only one-third (n = 32, 33.3%) of the patients underwent MWA-TACE containing DHL without other chemotherapeutic drugs during the operation. Of these patients, 51 (53.1%) patients underwent subsequent treatment, including repeated MWA-TACE with DHL, other therapies such as Iodine-125 seed implantation, systemic treatment and TACE. Of these, 20 (44.4%) patients in the PLC group and 8 (15.7%) patients in the MLC group underwent repeated MWA-TACE with DHL.

3.2. Safety

AEs related to treatment are shown in Table 2. Seventy-one AEs, mainly including abdominal pain, fever, vomiting and new ascites, were observed in 40 (41.7%) patients. Eight (8.3%) patients developed grade 3 AEs, all of whom received corresponding symptomatic treatments. No treatment-related death or grade 4 AEs occurred during the study period.

Laboratory tests before and 4–6 weeks after treatment are summarized in Table 3. Statistical differences were observed in serum total bilirubin level and neutrophil to lymphocyte ratio before and after treatment, both of which increased after treatment compared to before treatment. The changes in other laboratory tests were not significantly different before and after treatment.

3.3. Survival

The follow-up duration ranged from 3.0 to 39.0 months in the study population, with a median of 12.6 months. During the follow-up, 9 (20.0%) patients in the PLC group and 15 (29.4%) patients in the MLC group died. The median OS was not reached in the PLC group or MLC group (Fig. 1). The median LTPFS was 14.5 (95% confidence interval [CI], 7.2–21.8) months in the PLC group and 10.7 (95% CI, 7.7–13.7) months in the MLC group.

3.4. Radiological response

Based on the mRECIST criteria, the 1-month and 3-month local tumor responses are presented in Fig. 2. The disease control rate reached more than 80% in the PLC group and MLC group. The 1-month and 3-month local tumor control rates were similar in the PLC group. The objective response rate and disease control rate at 1 month after treatment can reach 68.9% and 86.7%, and those at 3 months after treatment can reach 70.7% and 85.4%. 12 (26.7%) patients in the PLC group and 6 (11.8%) patients in the MLC group had a complete response, and 19 (42.2%) patients in the PLC group and 24 (47.1%) patients in the MLC group had a partial response at 1 month after treatment.

Table 2
Adverse events related to treatment.

Variable	All events	Grade 1–2 events	Grade 3 events
Abdominal pain	16 (16.7)	14 (14.6)	2 (2.1)
Fever	10 (10.4)	9 (9.4)	1 (1.0)
Vomiting	12 (12.5)	12 (12.5)	0
Diarrhea	2 (2.1)	2 (2.1)	0
Liver abscess	1 (1.0)	0	1 (1.0)
Jaundice[a]	3 (3.1)	2 (2.1)	1 (1.0)
New ascites	7 (7.3)	6 (6.3)	1 (1.0)
Stomatitis	5 (5.2)	5 (5.2)	0
leukocytopenia	3 (3.1)	3 (3.1)	0
Platelet count decrease[b]	2 (2.1)	1 (1.0)	1 (1.0)
Absolute neutrophil count decrease[c]	4 (4.2)	3 (3.4)	1 (1.0)
Anemia	2 (2.1)	2 (2.1)	0
Hand-foot syndrome	4 (4.2)	4 (4.2)	0

[a] This indicates a transient increase in serum total bilirubin level of >3 mg/dL (51.3 μmol/L) after treatment without bile duct injury.
[b] This indicates a transient decrease in platelet count of $<75 \times 10^9$/L after treatment.
[c] This indicates a transient decrease in absolute neutrophil count of $<1.5 \times 10^9$/L after treatment.

Table 3
Laboratory tests before and 4–6 weeks after treatment.

Laboratory test	Pretreatment	4–6 weeks after treatment	*P* value[a]
Total bilirubin (μmol/L)	12.2 ± 6.3	20.9 ± 41.6	**0.006**
Albumin (g/L)	42.3 ± 4.8	41.4 ± 5.4	0.126
Alanine transaminase (U/L)	31.3 ± 27.6	37.4 ± 44.0	0.354
Aspartate aminotransferase (U/L)	37.8 ± 42.0	42.4 ± 52.6	0.499
Prothrombin time (s)	12.2 ± 1.2	12.5 ± 1.6	0.221
International normalized ratio	1.1 ± 0.1	1.1 ± 0.1	0.163
Red blood cell count (x 10^{12}/L)	4.4 ± 0.7	4.3 ± 0.7	0.470
Hemoglobin (g/L))	133.4 ± 21.5	130.1 ± 23.0	0.215
Platelet count (x 10^9/L)	181.0 ± 91.1	180.3 ± 91.6	0.993
White blood cell count (x 10^9/L)	5.8 ± 2.4	6.2 ± 3.7	0.558
Neutrophil to lymphocyte ratio	3.0 ± 2.5	4.1 ± 5.1	**0.043**

[a] Wilcoxon signed-rank test was used for statistical analyses.

4. Discussion

Currently, traditional chemotherapeutic drugs face problems such as lack of specificity, cytotoxicity, the occurrence of multi-drug resistance and short half-life.[7,16] To overcome these disadvantages, nanodrugs have attracted increasing attention in cancer therapy. Doxorubicin hydrochloride liposome, one of the most commonly used nanodrugs, has been widely used to treat some solid tumors in clinical practice.[17–19]

In the present study, we initially used DHL via the hepatic artery administration to combine MWA with TACE in patients with primary or metastatic liver cancer. Similar to other studies of MWA combined with TACE using traditional chemotherapeutic drugs, our results revealed that the combination therapy using DHL could inhibit local tumor progression, with a median LTPFS of 14.5 months in patients with primary liver cancer and 10.7 months in patients with metastatic liver cancer. Li et al.[20] reported that MWA and TACE using oil-epirubicin emulsion could provide a survival benefit in patients with hepatocellular carcinoma beyond the Milan criteria. The median progression-free survival and overall survival were 317 days and 1488 days, respectively. Two retrospective studies also indicated that the combination therapy of MWA and TACE using traditional chemotherapeutic drugs was safe, well-tolerated and effective in patients with hepatocellular carcinoma and liver metastases.[12,21] Our study also demonstrated that patients with primary and metastatic liver cancer had a good disease control rate, with all more than 80%. Thus, DHL might be an effective alternative drug to combine MWA with TACE when traditional chemotherapeutic drugs are intolerable in patients with liver cancer.

Until now, there is no recommendation in regard to the optimal drugs for TACE. Some clinical trials had attempted to compare epirubicin and platinum drugs for TACE and failed to achieve significant superiority.[22,23] A study involving 148 patients with unresectable hepatocellular carcinoma showed that TACE with raltitrexed plus liposomal doxorubicin had better clinical efficacy and lower occurrence rates of AEs than TACE with tegafur plus pirarubicin.[24] This may imply that liposomal doxorubicin has benefits when combined with other drugs or therapies.

In this study, the use of MWA has several advantages. First, hyperthermia can augment chemotherapy, which in turn, enhances ablation efficiency.[25] Compared with other thermal modalities, MWA has the characteristics of rapid temperature achievement, a larger ablation zone and low susceptibility to the heat-sink effect for cancer therapy.[26] Second, liposomal formulations such as DHL have been shown to circulate in the blood for an extended period and erupt due to the enhanced permeability retention (EPR) effect, which ensures that the formulation

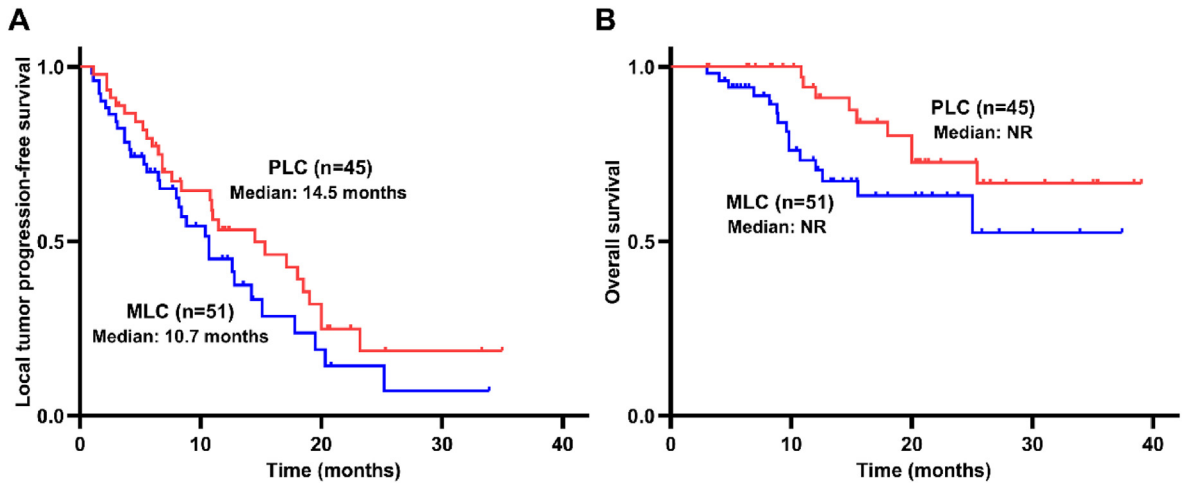

Fig. 1. Survival curves of local tumor progression-free survival (A) and overall survival (B) between the PLC and MLC groups.

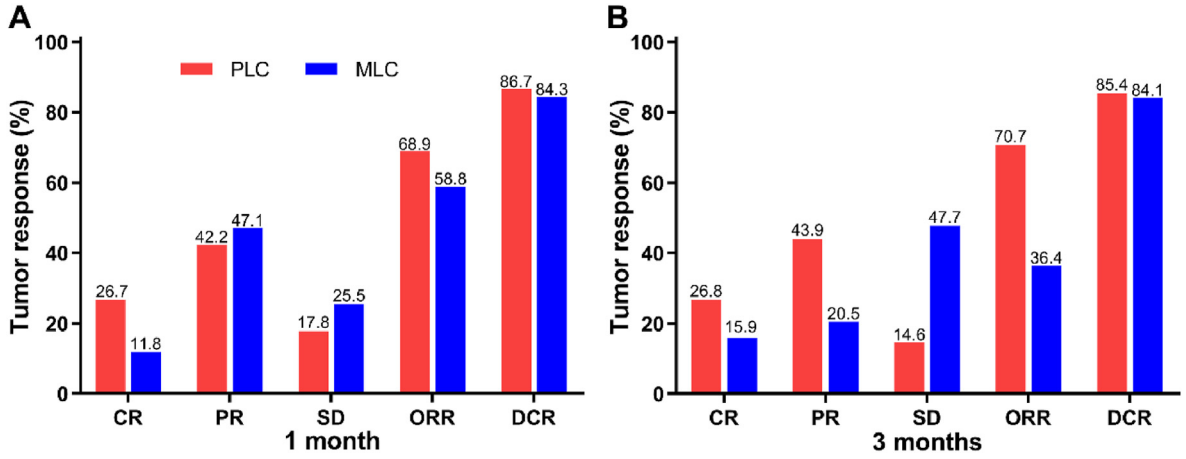

Fig. 2. Local tumor response rate at 1 month (A) and 3 months (B) after treatment. PLC, primary liver cancer; MLC, metastatic liver cancer; CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate.

remains in the tumor for as long as possible.[16,27] The delivery system of the tumor-feeding artery can increase intratumoral drug concentration. Meanwhile, heat in the tumor area after ablation can further induce the release of chemotherapeutic drugs.[28] Yang et al.[29] reported that thermosensitive liposomal doxorubicin combined with radiofrequency ablation could increase tumor destruction and improve survival in patients with medium and large hepatocellular carcinoma. These findings indicated that thermal ablation combined with liposomal formulations might improve the clinical efficacy of cancer therapy. Third, the overdose of chemotherapeutic drugs can increase systemic toxicity, and low doses of which can lead to poor efficacy. The potential mechanisms of MWA and synchronous TACE include decreased doses of lipiodol and chemotherapeutic drugs and minimal liver function damage with maximum tumor necrosis.[30,31]

Our study suggested that DHL, in combination with MWA and TACE, was safety and manageable for the treatment of primary or metastatic liver cancer. The most common AEs related to treatment included post-embolization syndrome (such as abdominal pain, fever without any infection focus and vomiting), new ascites and stomatitis, which may be mainly caused by embolization or ablation rather than the nanodrug. In addition, all AEs were relieved after the corresponding treatment or improvement of the patient's status.

The study has several limitations. First, the pharmacokinetic profile of doxorubicin hydrochloride liposome was not detected and evaluated in this study. Traditional small molecule drugs such as doxorubicin and epirubicin were not designed for a control group. And then, the study population included primary and metastatic liver cancer rather than a specific type of liver cancer, which may lead to a certain bias.

In conclusion, our study preliminarily confirmed the safety and promising outcomes of the treatment with MWA and TACE containing doxorubicin hydrochloride liposome for primary and metastatic liver cancer. Doxorubicin hydrochloride liposome was considered a potential alternative drug for TACE. This may need to be further confirmed in a large sample, prospective randomized controlled trials.

Declaration of competing interest

Zhiping Yan is Aaaociate Editors-in-chief for Journal of Interventional Medicine and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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