Ultrasensitive transcatheter infusion of epirubicin in water-in-oil-in-water emulsion for small hepatocellular carcinoma

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Objective: We have previously reported the clinical efficacy of water-in-oil-in-water (W/O/W) emulsions, particularly for non-selective transcatheter arterial infusion (TAI) therapy. W/O/W emulsions limit damage to normal hepatic parenchyma, because of their minimal embolic effect on peripheral arteries and slow release of anticancer agent. The purpose of this study was to evaluate the safety and effectiveness of ultrasensitive TAI (UTI) of a W/O/W emulsion for hepatocellular carcinoma (HCC).

Methods: 11 patients with Stage I–III small HCCs (<5 cm) underwent UTI with a W/O/W emulsion at our institute. Response was assessed using the Response Evaluation Criteria in Solid Tumors. Disease-free survival time was estimated using the Kaplan–Meier method.

Results: All 10 patients, excluding a patient who underwent a hepatectomy after UTI, achieved complete response. The 6, 12 and 30 month cumulative disease-free survival rates for the 10 patients were 100%, 90% and 60%, respectively. The patient who underwent hepatectomy after UTI developed complete necrosis of the HCC and peritumoral non-tumorous liver parenchyma.

Conclusion: UTI therapy using a W/O/W emulsion for patients with small HCCs results in a good local response.

Received 13 June 2011
Revised 20 August 2011
Accepted 30 August 2011

DOI: 10.1259/bjr/16376960

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Radiology

A water-in-oil-in-water (W/O/W) emulsion is a unique material that is advantageous because of its minimal embolic effect on peripheral arteries and a slow, sustained release of anticancer agent [1–4]. For that reason, transcatheter arterial infusion (TAI) of a W/O/W is particularly useful for patients with recurrent hepatocellular carcinoma (HCC) following surgical resection, as well as for those with multifocal lesions or liver dysfunction [5]. A W/O/W emulsion can also be safely infused via parasitic arteries, including the cystic artery, without the concern of damaging other organs [6]. A W/O/W emulsion is believed to be useful for non-selective TAI therapy rather than for selective TAI therapy. The purpose of the present study was to evaluate the effectiveness of ultrasensitive TAI (UTI) of epirubicin in a W/O/W emulsion for HCCs <5 cm.

Methods and materials

Epirubicin in a water-in-oil-in-water emulsion

A W/O/W emulsion was prepared measuring 15 ml, and containing 60 mg epirubicin dissolved in 5 ml of 5.8% glucose solution as the inner aqueous phase, 5 ml lipiodol containing 500 mg polyglycerol esters of polycondensed fatty acids of castor oil as the oily phase, and physiological

saline with polyoxyethylene 60 stearate. Lipiodol micro-droplets of a uniform size and a median diameter of 70 µm were used (Figure 1) [3]. Figure 2 shows how to prepare a W/O/W emulsion.

Patients

11 patients with Stage I–III small HCCs (<5 cm) underwent UTI with a W/O/W emulsion at our institute. Table 1 summarises the clinical data of these patients. The HCC diagnosis was confirmed by early enhancement and a delayed washout pattern on dynamic contrast-enhanced CT (CE-CT) and high serum levels of the tumour markers α -fetoprotein (>20 ng ml⁻¹) and protein induced in the absence of vitamin K II (>40 mAU ml⁻¹). Infusion of the emulsion was stopped when the tumour stain disappeared on subsequent selective arteriography. The mean diameter of the HCCs was 24 ± 14 mm (range, 10–45 mm). In all patients, 5–14 ml of the W/O/W emulsion was infused ultra-selectively. The use of a W/O/W emulsion was approved by our institutional review board, and informed consent was obtained from all patients. We retrospectively analysed the safety and effectiveness of UTI of W/O/W emulsion. Before treatment, all patients were evaluated by hepatobiliary surgeons and interventional radiologists, and were determined to be appropriate candidates based on a review of lesion morphology, underlying liver function and comorbid disease. Absolute contraindications for UTI included

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Figure 1. Optical microphotograph of a water-in-oil-in-water emulsion prepared with a controlled-pore glass membrane. The lipiodol microdroplets, containing many vesicles of an aqueous epirubicin solution, were suspended in the external aqueous phase. The median diameter of the lipiodol microdroplets was 70 μm .

hepatic encephalopathy, uncorrectable coagulopathy and Child–Pugh Class C.

Interventional procedure

Hepatic angiography was performed via a common femoral approach using a 4Fr angiographic catheter (Twist B; Medikit, Tokyo, Japan). After locating the lesion by selective arteriography using a 2.0–2.7Fr microcatheter (Meistercath selective type or Meistercath high flow type, Medikit; Sniper II selective type; Terumo Clinical Supply, Kagamigahara, Japan), a W/O/W emulsion was infused via a feeding arteries. Gelatin sponge particles were not used in any patient.

Evaluations

The response to UTI therapy was assessed by dynamic CE-CT at 4 weeks and 3 months after UTI. Response was assessed using the Response Evaluation Criteria in Solid Tumors [7]: CR, complete response, disappearance of

all target lesions; PR, partial response, at least a 30% decrease in the sum of the longest diameters (LDs) of target lesions; PD, progressive disease, at least a 20% increase in the sum of the LDs of target lesions; and SD, stable disease, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Complications were graded according to the Common Terminology Criteria for Adverse Events (version 3) [8]. As per the criteria, Grade I complications were designated as those requiring no intervention, but included asymptomatic vascular complications. Grade II complications included those requiring bedside medical management, bacteraemia requiring intravenous antibiotics and cardiovascular arrhythmias requiring additional medication. Grade III complications required observational intervention in a monitored setting or extended therapy. Grade IV complications resulted in some form of chronic disability. Grade V complications included periprocedural deaths. Disease-free survival time was estimated using the Kaplan–Meier method.

Results

One patient underwent a hepatectomy 20 days after UTI and demonstrated complete necrosis of the HCC and peritumoural non-tumorous liver parenchyma (Figure 3). Another 10 patients (Figures 4 and 5) achieved a CR. Their 6, 12 and 30 month cumulative disease-free survival rates were 100%, 90% and 60%, respectively (Figure 6). Six complications were noted. Three were of Grade II, including hypotension requiring medication and episodes of prolonged fever, whereas the other three were Grade I, and included hypotensive episodes requiring no intervention. The follow-up period ranged from 18 to 36 months. One patient died because of a rupture of oesophageal varices within 19 months after treatment.

Discussion

In general, transarterial chemoembolisation (TACE) for HCC is a palliative therapy for unresectable HCC particularly multifocal lesions [9–11]. Ultrasensitive

Figure 2. Preparation of water-in-oil-in-water emulsion (W/O/W) by a membrane emulsification technique. The aqueous solution of epirubicin was mixed with lipiodol containing tetraglycerine-condensed ricinoleate. The mixture was sonicated to form water-in-oil emulsion (W/O), which was filled in the upper chamber of the module. Nitrogen gassed at a pressure of 54 kPa into the upper chamber initiated a permeation of W/O through the controlled-pore glass membrane into the emulsifying chamber forming W/O/W.

Table 1. Summary of clinical data of 11 patients

Characteristic	Data
Age (mean $\pm$ SD; years)	69 $\pm$ 12
Gender: male/female	9/2
Cirrhosis: yes/no	3/8
Aetiology: HBV/HCV/unknown	7/4/0
HCC Stage: I/II/III	2/5/4

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SD, standard deviation.

transcatheter arterial chemoembolisation, which is defined as TACE from the distal portion of the feeding subsegmental hepatic artery to induce a subsegmentectomy-like

effect, is considered a curative therapy that can attain good local control [12–14]. Miyayama et al [14] reported that local recurrence is significantly lower when a greater degree of portal vein visualisation is demonstrated during ultraselective TACE because the lipiodol flows into the surrounding portal vein. They also reported that ultraselective TACE has therapeutic effects strong enough to induce necrosis of non-tumorous liver parenchyma, using histopathological analysis in patients who underwent surgical hepatic resection after TACE [15].

A W/O/W emulsion, which is a unique drug delivery system reported first by Higashi et al [1–4], is effective for managing HCC. A W/O/W emulsion has a minimal

Figure 3. A 54-year-old male with Stage II hepatocellular carcinoma (HCC). (a) Angiography before ultraselective transcatheter arterial infusion (UTI) showing tumour staining fed by A6 (arrow). (b) The tumour stain disappeared on angiography after the UTI. (c) Lipiodol accumulation was demonstrated densely in the HCC on plain CT and the peritumoural hepatic parenchyma was not enhanced on contrast-enhanced CT (arrow) 7 days after UTI. (d) Resected specimens demonstrated complete necrosis of the tumour and the surrounding non-tumorous liver parenchyma.

Figure 4. A 77-year-old male with Stage I hepatocellular carcinoma (HCC). (a) Angiography before the ultraslective transcatheter arterial infusion (UTI) showing tumour staining fed by A8 (arrow). (b) Dense lipiodol accumulation was demonstrated in the HCC on plain CT 7 days after UTI. (c) 4 months later, the HCC was infarcted on contrast enhanced CT.

Figure 5. A 70-year-old male with Stage I hepatocellular carcinoma (HCC). (a) A tumour stain occurred in S5 on early phase contrast-enhanced CT (arrow). (b) Angiography before the ultraslective transcatheter arterial infusion (UTI) showing tumour staining fed by A5 (arrow). (c) A tumour stain was demonstrated on selective arteriography via A5. (d) Lipiodol accumulation was demonstrated densely in the HCC and mildly in the hepatic parenchyma below the HCC 7 days after UTI (arrows). (e) 3 months later, the HCC had decreased in size and the hepatic parenchyma below the HCC was infarcted on contrast-enhanced CT (arrows).

Figure 6. Kaplan-Meier curve showing cumulative disease-free survival rates after ultraselective transcatheter arterial infusion (UTI).

embolic effect on the peripheral hepatic artery, and washout from the normal parenchyma occurs rapidly. However, the emulsion is effectively trapped in the HCC. The release of anticancer agents from lipiodol in a W/O/W emulsion is slow because the agent is contained within the lipiodol microdroplets, whereas in a conventional lipiodol emulsion it is contained in the external aqueous solution. Owing to these unique features of a W/O/W emulsion, we have already reported that transcatheter arterial infusion of a W/O/W emulsion is a good therapeutic option for patients with recurrent HCC following surgical resection and for those with multifocal HCC or liver dysfunction [5]. We also reported that the direct infusion of a W/O/W emulsion via the cystic artery is an effective and easy procedure for treating cases of HCC fed by the cystic artery with minimal risk of gallbladder damage, because when a W/O/W emulsion is infused via this artery, washout occurs rapidly from the gallbladder, and the anticancer agent is released slowly from the lipiodol [6]. We believed that a W/O/W emulsion was more suitable for non-selective than for selective infusion therapy.

When using ultraselective TACE, lipiodol is supposed to flow into the surrounding portal venules and hepatic sinusoids through the peribiliary plexus and drain from the HCC [16]. According to this hypothesis, the W/O/W emulsion, which has a uniformly sized microdroplet of about 70 µm diameter, is predicted to enter the peribiliary plexus easily. Therefore, a W/O/W emulsion may be an effective material for UTI therapy for HCC. The effectiveness of UTI with a W/O/W emulsion was assessed retrospectively in a preliminary study. According to Matsui et al [12], they performed subsegmental transcatheter arterial chemoembolisation in 100 patients with HCCs <4 cm in diameter and achieved 1- and 4-year local recurrence rates of 18% and 33%, respectively, as well as 1- and 4-year survival rates of 100% and 67%, respectively. Takayasu et al [13] performed targeted transarterial oily chemoembolisation in 54 patients with HCCs <5 cm, using a unified helical CT and angiography system. In their report, local recurrence was 33.2% at 1 year and 37.8% at 2 and 3

years. The survival rates at 1, 2 and 3 years were 93.3%, 77.1% and 77.1%, respectively. Miyayama et al [14] performed ultraselective TACE with a 2-Fr tip microcatheter in 72 patients with HCCs <5 cm in diameter. In their report, local recurrences were 13.0%, 25.6%, 31.2%, 34.7%, 34.7% and 34.7% at 6, 12, 18, 24, 30 and 36 months, respectively.

In our preliminary study, disease-free survival rates of 100%, 90% and 60% at 6, 12 and 30 months, respectively, were comparable with these reports. Our study is a preliminary retrospective study with a small sample size and has no controls. However, the results suggest the possible usefulness of a W/O/W emulsion for UTI therapy of HCC as well as for non-selective infusion therapy. Further larger randomised prospective controlled studies are needed to evaluate the effectiveness of UTI with a W/O/W emulsion for HCCs.

Conclusion

Favourable disease-free survival was obtained by UTI using a W/O/W emulsion. A W/O/W emulsion may also be a good option for UTI for focal HCCs.

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