Original Article

^{131}Iodine-DEM TACE *vs.* conventional TACE in cirrhotic patients with hepatocellular carcinoma: a single center experiment

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Background: To evaluate the safety and efficacy of transcatheter arterial chemoembolization (TACE) with ^{131}iodine-doxorubicin-eluting gelatin microspheres (^{131}I-DEM TACE) compared with conventional TACE (cTACE) with polyvinyl alcohol foam (PVA) embolization microspheres.

Methods: A total of 22 patients diagnosed with hepatocellular carcinoma were equally divided into 2 groups. The patients who underwent TACE with ^{131}I-DEM (25.7×10^7 Bq of 131iodine and 10 mg of doxorubicin) were compared to controls who received cTACE with PVA embolization microspheres. Therapeutic effects were evaluated by the tumor regression rates, levels of alpha-fetoprotein in serum, survival rates, and complications.

Results: The operative complications of the 2 groups were not significantly different (P=0.753). The radioactivity ratio of the tumor to the liver was approximately 4.1:1 for the ^{131}I-DEM TACE group. In the ^{131}I-DEM TACE group, 54.5% of patients achieved tumor regression of more than 50%, compared to 36.6% of patients in the cTACE group. AFP levels in serum declined in 100% of patients in the ^{131}I-DEM TACE group and 50% of patients in the cTACE group. The median survival time of the patients was 12.0±3.3 months for the ^{131}I-DEM TACE group and 10.0±3.3 months for the cTACE group. There were no significant differences in survival between the 2 groups (P=0.414).

Conclusions: ^{131}I-DEM may become a potential radiochemoembolization agent to treat patients with unresectable hepatocellular carcinoma through TACE.

Keywords: Transcatheter arterial chemoembolization (TACE); ^{131}Iodine; anticancer; hepatocellular carcinoma (HCC); microspheres

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Introduction

Hepatocellular carcinoma (HCC) is a significant medical burden in China. Of the 841,000 new cases worldwide every year (1), China accounts for approximately 392,868 cases. The annual death toll from HCC in China is approximately 368,960, making it the third most deadly type of malignant

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tumor in the country (2). Because the prognosis of HCC is generally poor, the natural survival time after confirmed diagnosis typically ranges from 2 to 4 months (3). Currently, surgical resection, with a 5-year survival rate ranging from 11% to 76%, remains the most popular therapeutic method (4). However, most HCC patients are not diagnosed until the terminal stage, and 90% of them have a background of chronic hepatitis B and hepatocirrhosis, leaving only 9–27% eligible for partial hepatectomy (5,6).

Ablative therapies for treating small HCCs, such as percutaneous ethanol injection and radiofrequency ablation, reportedly have similar effects to surgery (7). However, radiofrequency is only suitable for smaller tumors, as it does not yield favorable results when the tumor diameter exceeds 5 cm (8).

Hepatic arterial embolization (HAE) for unresectable HCC cases has developed rapidly in recent years. HAE can obstruct the arteries that supply HCC by interventional therapy which lead to the tumor necrosis. It is appropriate for most cases, and many trials have shown that HAE alone or in combination with portal vein embolization is safe and effective in the treatment of primary and metastatic liver tumors (9-12). Years of clinical observation have revealed that the effects of HAE mainly depend on the type of embolization material. While materials that merely block blood flow, such as a gelatin sponge, steel wire mesh, and poly-L-lactic acid, are reported to be effective, novel embolic agents that accomplish both embolization and other antitumor effects have attracted more attention in recent years. Transcatheter arterial chemoembolization (TACE) is known as an effective method of treating advanced HCC that is ineligible for resection (13). Common materials used to obstruct the arteries that supply the tumor are lipiodol, chemotherapeutic drugs, and polyvinyl alcohol foam (PVA) embolization particles. In recent years, new embolic materials have been developed and treatment has progressed to such combination regimens as chemoembolization, radioembolization, and immunoembolization, which have been shown to significantly improve the prognosis of HCC (14). As a drug for targeted therapy, ^{131}iodine metuximab injection is reportedly safe and effective. However, the retention of ^{131}iodine in the tumor has not been as high as expected (15).

Given these favorable aspects, and the disadvantages of current materials for TACE, we produced doxorubicin-eluting gelatin microspheres (GM) labeled with radioactive ^{131}iodine (^{131}I-DEM) at high concentrations for TACE (16). As embolism materials, these microspheres are multifunctional, which has both functions of drug elution and internal radiation. In this drug-eluting microspheres, ^{131}iodine is chemically bonded to gelatin and eluted as the gelatin microspheres degrade. According to the previous study, it takes approximately one month for the GM to degrade (17). Therefore, the ^{131}iodine in GM eluted more slowly and have a longer stagnation time in liver tumors than ^{131}iodine metuximab injection, which is likely to achieve better radiotherapy results. After demonstrating safety in animal experiments (18), we carried out a preliminary trial of TACE with ^{131}iodine-doxorubicin-eluting gelatin microspheres (^{131}I-DEM) in 11 patients with unresectable HCC. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-21-105).

Methods

Patient selection

The clinical data of 11 patients with HCC who underwent TACE with ^{131}I-DEM (^{131}I-DEM TACE group) and 11 patients with HCC treated with conventional TACE (cTACE) from April 2008 to October 2010 at our center were retrospectively analyzed. The median duration of follow-up was 12.34±7.27 months (3–29 months). The study was approved by the ethics committee of West China Hospital, Sichuan University, and each participant fully understood the possible risks, benefits, and other options they may have had, and provided written informed consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). All patients in the ^{131}I-DEM TACE group took Lugol's iodine at least 3 days before the operation to avoid potential damage to the thyroid gland. Patients in the 2 groups had a confirmed diagnosis of HCC by radiological findings and alpha-fetoprotein (AFP) levels in serum according to the Barcelona criteria. The inclusion criteria of our study were: (I) diagnosis of HCC, confirmed by evidence of elevated AFP (over 400 ng/mL) and characteristic imaging of HCC from either computed tomography (CT) or magnetic resonance imaging (MRI), or 2 sorts of imaging evidence (both CT and MRI) with AFP over 200 ng/mL; (II) patients with HCC whose liver function was Child-Pugh Class A or B, and bilirubin <51 μmol/L; (III) patients with HCC who were not suitable for hepatectomy, transplantation, and percutaneous

ablation according to consultations with all surgeons at the Department of Hepatic Surgery; (IV) no previous TACE or other treatment. The exclusion criteria were: evidence of extrahepatic metastasis, infection, coagulation dysfunction, and other contraindications for intervention therapy. The end points were adverse clinical events or time to progression.

Preparation of ^{131}I-DEM

GMs with an average diameter of 70 μm (range, 45 to 120 μm) were produced according to the modified method of Tabata and Ikaba (19). Briefly, GMs were combined with ^{131}I using the chloramines-T method, and the ^{131}I-GMs were dried with a freeze dryer, sterilized by ^{60}Co radiation, and sealed in ampules for later use. Before injection, the ^{131}I-GMs were soaked in normal saline containing 10 mg of doxorubicin for 15 minutes so that they could absorb enough doxorubicin and swell (20). We then obtained the ^{131}I-DEM for administration.

Hepatic artery infusion

The patients were subjected to ^{131}I-DEM TACE or cTACE using Seldinger's method under local anesthesia (21). Catheters were placed in the proper hepatic artery in 13 patients and selectively placed in the left or right branch of the proper hepatic artery in the other 9 patients before infusion of the microspheres. We then infused 10 mL lipiodol and 100–200 mg of ^{131}I-DEM with an average radioactivity of 25.7×10^7 Bq (varied from 14.4 to 44.4×10^7 Bq according to the tumor size) for each patient in the ^{131}I-DEM TACE group, or 10 ml of lipiodol with 10 mg of doxorubicin and approximately 300 PVA-100 embolization particles (Cook Medical. Inc, Bloomington, USA) for each patient in the cTACE group.

Evaluation

All patients of both groups were hospitalized for observation for 1 week after the procedure. Patients were regularly followed up for CT scans, AFP levels, and liver function tests every 3 months. Pathological changes and reductions in tumor size were examined with liver CT scans within 3 months. All clinical data on deaths were analyzed to confirm the direct causes of death. Single photon emission computerized tomography (SPECT) scans of the liver and thyroid on days 7 and 14 after the operation for patients in the ^{131}I-DEM TACE group were performed, through which the distribution of microspheres, the radioactivity ratio of the tumor to the normal liver tissue, ectopic embolism, and the radiation distribution in the thyroid gland were observed and calculated.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (version 22.0; SPSS, Inc., Chicago, IL, USA). Values for all continuous variables are quoted as mean, standard deviation, and minimum and maximum throughout. The paired *t*-test was used to demonstrate changes in biochemistry over time. The Kaplan-Meier method with the log-rank test was used to compare the survival rates of the 2 groups. A P value <0.05 was considered significant.

Results

Preoperative clinical data from the 2 groups

The study included 13 males and 9 females. As shown in *Table 1*, the ^{131}I-DEM TACE group and the cTACE group had similar preoperative characteristics, including age in years (51.0±10.1 and 51.3±10.0, respectively; P=0.94), tumor size (9.2±2.9 and 9.0±3.2 cm, respectively; P=0.931), albumin (ALB) levels (37.1±5.0 and 35.5±5.0 g/L, respectively; P=0.503), and alanine aminotransferase (ALT) levels (45.3±29.8 and 54.6±27.2 IU/L, respectively; P=0.320). CT and MRI scans revealed a cancer embolus in 4 cases of the ^{131}I-DEM TACE group and 7 cases in the cTACE group. AFP levels over 400 ng/ml were found in 7 cases of the ^{131}I-DEM TACE group and 6 cases in the cTACE group.

Outcomes

All patients were discharged successfully. Post-embolization syndrome, including moderate fever, hiccups, elevated white blood cell count, and increased plasma ALT, was observed in most patients 1 or 2 weeks after the operation in both groups. Moderate jaundice occurred in 3 cases of the ^{131}I-DEM TACE group and 4 cases of the cTACE group. In the ^{131}I-DEM TACE group, 1 case vomited coffee-colored gastric fluid, which was alleviated by fasting and administration of an H2 receptor blocker (*Table 2*).

For the ^{131}I-DEM TACE group, clear contours of tumors

Table 1 Clinical characteristics of the subjects

Parameters	^{131}I-DEM TACE group (n=11)	cTACE group (n=11)	P value
Age (years)	51.0±10.1	51.3±10.0	0.94
Sex (male)	7/11	6/11	
Size (cm)	9.2±2.9	9.0±3.2	0.931
APF over 400 ng/mL	7/11	6/11	
ALB (g/L)	37.1±5.0	35.5±5.0	0.503
ALT (U/L)	45.3±29.8	54.6±27.2	0.320
Cancer embolus	4	7	

^{131}I-DEM TACE, transcatheter arterial chemoembolization with ^{131}iodine-doxorubicin-gelatin microspheres; cTACE, conventional TACE; ALT, albumin.

Table 2 Complications after administration

Complications	^{131}I-DEM TACE group	cTACE group	P value
Fever	8	7	
Hiccups	5	5	
WBC increase	11	10	
ALT increase	11	9	
Hyperbilirubinemia	3	4	
Pneumonia	0	0	
Wound infection	0	0	
Stress ulcer	1	0	
Total	39	35	0.753

^{131}I-DEM TACE, transcatheter arterial chemoembolization with ^{131}iodine-doxorubicin-gelatin microspheres; cTACE, conventional TACE; ALT, albumin.

were observed on postoperative SPECT. The tumor/liver radioactivity ratio was 4.1±1.11:1 (varied from 2.3:1 to 6.5:1) (*Figure 1A*). No radionuclide was observed in the thyroid region through SPECT. However, mild extrahepatic radioactivity was found in the patient with coffee-like vomitus, and the SPECT scanning suggested blood backstreaming to the stomach and spleen. AFP levels were significantly reduced in 7 AFP-positive patients of the ^{131}I-DEM TACE group and 3 patients of the cTACE group at day 30 after administration. CT findings on countercheck 3 months after the operation indicated that for the ^{131}I-DEM TACE group, tumors had reduced markedly, with prominent necrosis in 9 patients. In 6 of these patients, the tumor diameters decreased by 50% (*Figure 1B,C*). However, for the cTACE group, tumors decreased by 50% in 4 patients (*Table 3*).

The survival rates of the 2 groups

The survival rates at 6 months, 1 year, and 2 years were, respectively, 72.72% (8/11), 63.63% (7/11), and 18.18% (2/11) for the ^{131}I-DEM TACE group, and 81.82% (9/11), 54.55% (6/11), and 0% (0/11) for the cTACE group. The median survival time was 12.0±3.3 months for the ^{131}I-DEM TACE group and 10.0±3.3 months for the cTACE group. For both groups, the leading cause of death within 6 months was liver failure due to deteriorated hepatocirrhosis. The main causes of death beyond 6 months included recurrent tumor, extrahepatic metastasis, and rupture and bleeding of the varicose esophagus vein. As shown in *Figure 2*, there was no significant difference in survival between the 2 groups (P=0.414).

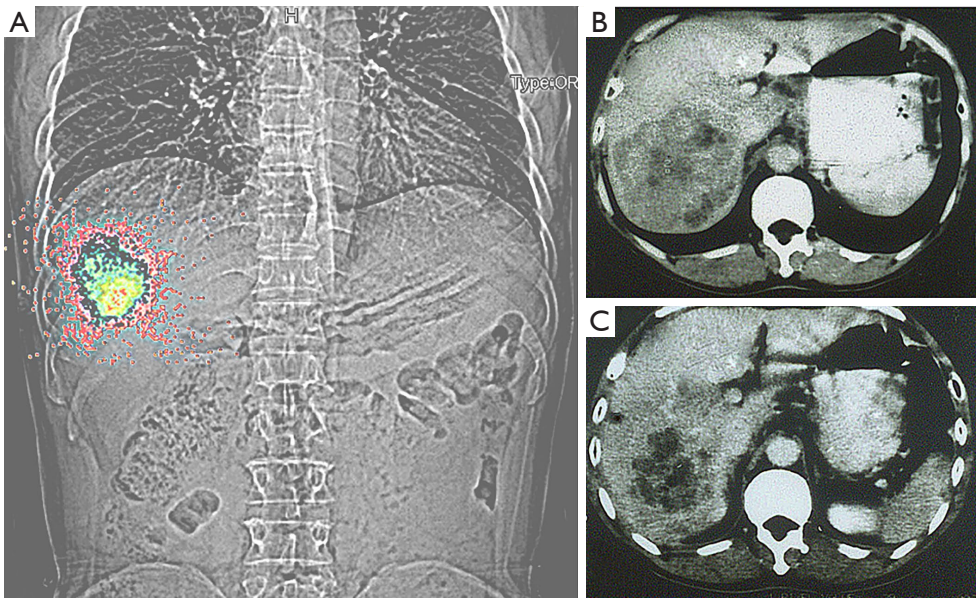

Figure 1 The tumor responded well to ^{131}I-DEM TACE. (A) SPECT photos taken 7 days after administration in a patient of ^{131}I-DEM TACE group showed that radioactive material has been gathered into the tumor, which showed in color on the image. (B) CT scan before operation showed a huge tumor in the right lobe of liver of a patient. (C) CT scan three months after operation showed significant necrosis of the tumor in the same patient who accepted therapy with ^{131}I-DEM TACE.

Table 3 Tumor response based on EASL criteria at 3-month follow-up

Outcome (3-month follow-up)	^{131}I-DEM TACE group, N (%)	cTACE group, N (%)
CR	0 (0.0)	0 (0.0)
PR	6 (54.5)	4 (36.3)
SD	5 (45.5)	7 (63.6)
PD	0 (0.0)	2 (18.2)
OR	6 (54.5)	4 (36.3)
AFP decrease	7/7 (100.0)	3/6 (50.0)
Death	1 (9.1)	0 (0.0)

^{131}I-DEM TACE, transcatheter arterial chemoembolization with ^{131}iodine-doxorubicin-gelatin microspheres; cTACE, conventional TACE; EASL, European Association for the Study of the Liver; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response.

Discussion

Evidence has shown that TACE can improve the survival of patients with unresectable HCC (22). In some previous studies, radioactive material comprised part of the embolic agents for TACE. Raoul *et al.* reported the ^{131}iodine-labeled iodized oil as a new agent. They reported that the survival rates at 6 months, 1, 2, 3, and 4 years were 69%, 38%, 22%, 14%, and 10%, respectively, which were not significantly different from conventional chemoembolization. However, there were fewer complications (23).

The ^{131}I-DEM we produced was a combined agent with a radionuclide and doxorubicin, as doxorubicin has been widely used for treating malignancies, and radionuclide microspheres have been adopted in arterial embolization of tumors by many researchers. Both of them have been confirmed to be beneficial in the prognosis of cancer patients (24).

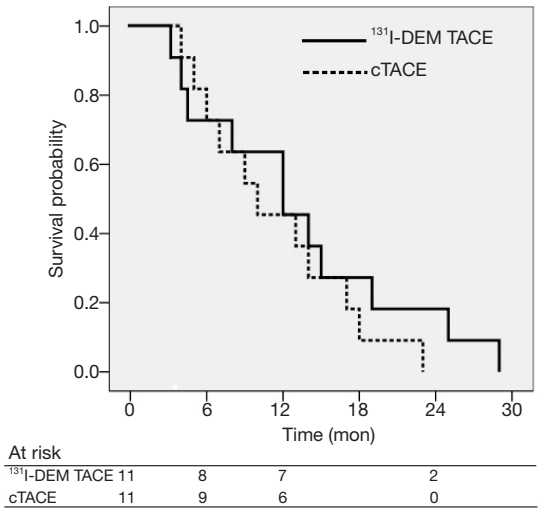

Figure 2 Though the patients of the ^{131}I-DEM TACE group showed a better survival time with time growth and the median survival time was 12.0 months in the ^{131}I-DEM group comparing with 10.0 months in the cTACE group, there is no significant statistic difference between the two groups (P=0.414).

Radionuclide microspheres and particles represent a new generation of drugs for the treatment of tumors via internal therapy by arterial embolization. A new sub-discipline, which combines the sciences of radiology and cancer therapy, has been advancing rapidly, as previous research has suggested far better outcomes of arterial embolization when combined with internal radiation compared to cTACE, and combined therapy reportedly achieved similar or even equal effects to surgical resection (25-29).

Gelatin is a degradable biomaterial with good biocompatibility. Preliminary studies as well as the present study have revealed some of the characteristics of ^{131}I-DEM: (I) favorable arterial embolization, where the rigid GMs remain in the small arteries in the liver after infusion via the hepatic artery. As an alien protein, gelatin activates fibroblasts and macrophages in blood vessels and surrounding tissues, which gradually wrap around the microspheres and cause fibrillation and embolism of the vasculature, resulting in long-term blockage of the blood stream (30,31). (II) High intratumoral concentration: as indicated in our study, most microspheres are retained in the tumor rather than distributed all over the liver or extrahepatic tissues, achieving a targeted radiation effect. (III) Gelatin adheres to various chemicals, including doxorubicin in our study, which are later continuously released when the microspheres gradually degrade in the tumor (32). (IV) Different from ^{90}yttrium and ^{32}phosphorus, which both release pure beta rays, ^{131}iodine additionally emits gamma rays that can be detected by a gamma camera or SPECT, and therefore the distribution of the microspheres and ectopic embolism can easily be identified.

Degradability of ^{131}I-GMs has the potential for radioactive contamination in the secondary distribution of ^{131}iodine in its degradation process, which particularly threatens the thyroid. However, our findings with SPECT showed no radiation accumulation in the thyroid, and decreased thyroid function was not observed in any of our cases. A possible explanation is that the thyroid gland was protected by the Lugol's iodine taken as a preoperative medication. Another possibility may be that the degradation of the microspheres takes 1 to 2 months, while the half-life of ^{131}iodine is only 8.04 days. When most microspheres degrade, the radioactivity of ^{131}iodine has already decreased considerably after 4–6 half-lives. Furthermore, ^{131}iodine labeling involves the oxidation of iodide into atomic iodine and its nucleophilic substitution into phenol rings at the ortho position located in the hydroxyl group of tyrosyl residues of gelatin (33). This suggests ^{131}iodine does not break freely from the amino acid when the protein degrades, and may thus be discharged in urine with the secondary degradation products rather than remaining in the human body in its free form.

In our study, patients in the ^{131}I-DEM TACE group had significantly higher radioactivity in tumors than in normal liver tissue, with an average ratio of 4.1±1.1:1. Additionally, 9 patients had at least a 20% reduction in tumor size, and in 6 of these patients, the tumor size was reduced by more than 50%. The response of the tumor was 81.82% (9/11) at 3 months, and the median survival time after administration was 12.0±3.3 months, which was better than the cTACE group. In our study, there were 3 patients with right portal vein tumor thrombi and 1 patient with an embolus in the middle hepatic vein in the ^{131}I-DEM TACE group, and 5 patients with a portal vein cancer embolus in the cTACE group. They had a shorter survival time compared with other patients, which was consistent with previous studies. Raoul *et al.* also reported that patients with portal vein thrombosis had a poor prognosis. Although patients were treated with intra-arterial ^{131}iodine-iodized oil, the survival rates at 3, 6, and 9 months were 71%, 48%, and 7%, respectively. However, the prognosis of the treated group was significant better than that of the control group, whose survival rates at 3, 6, and 9 months were 10%, 0%, and 0%,

respectively (34).

Though ^{131}I-DEM TACE may bring patients better efficacy, there are some limitations. ^{131}iodine in ^{131}I-DEM would increase radiation damage to doctors and patients. This intervention operation needs long time to complete, so the radioactive rays from ^{131}iodine expose the physician to the harmful radiation. The physicians need to wear heavy protective vests which may cause inconvenience while operating. The patients should also stay in radiation protection ward after operation until the radioactivity in the body decline below 400 MBq. This will increase the patients' hospital stay and expense.

In summary, our investigation verified the feasibility of the described therapy. The favorable biocompatibility, degradability, and the ability to combine with a variety of drugs and radionuclides make GMs a preferred carrier for radioactive and chemotherapeutic antitumor agents, achieving the effects of both internal radiation and targeted chemotherapy. However, its efficacy and complications were not fully evaluated due to the number of cases as a pilot study. Controlled trials with larger sample are therefore needed to further investigate its efficacy and safety before this new combined therapy can be recommended for patients with unresectable HCC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethics committee of West China Hospital, Sichuan University, and each participant fully understood the possible risks, benefits, and other options they may have had, and provided written informed consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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