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RAPID COMMUNICATION

Efficacy of transcatheter embolization/chemoembolization (TAE/TACE) for the treatment of single hepatocellular carcinoma

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Abstract

AIM: To investigate the efficacy of transcatheter embolization/chemoembolization (TAE/TACE) in cirrhotic patients with single hepatocellular carcinoma (HCC) not suitable for surgical resection and percutaneous ablation therapy.

METHODS: A cohort of 176 consecutive cirrhotic patients with single HCC undergoing TAE/TACE was reviewed; 162 patients had at least one image examination (helical CT scan or triphasic contrast-enhanced MRI) after treatment and were included into the study. TAE was performed with Lipiodol followed by Gelfoam embolization; TACE was performed with Farmorubicin prepared in sterile drip at a dose of 50 mg/m^2, infused over 30 min using a peristaltic pump, and followed by Lipiodol and Gelfoam embolization.

RESULTS: Patients characteristics were: mean age, 62 years; male/female 117/45; Child-Pugh score 6.2 ± 1.1; MELD 8.7 ± 2.3; mean HCC size, 3.6 (range 1.0-12.0) cm. HCC size class was ⩽ 2.0 cm, *n* = 51; 2.1-3.0 cm, *n* = 35; 3.1-4.0 cm, *n* = 29; 4.1-5.0 cm, *n* = 22; 5.1-6.0 cm, *n* = 11; and > 6.0 cm, *n* = 14. Patients received a total of 368 TAE/TACE (mean 2.4 ± 1.7). Complete tumor necrosis was obtained in 94 patients (58%), massive (90%-99%) necrosis in 16 patients (10%), partial (50%-89%) necrosis in 18 patients (11%) and poor (< 50%) necrosis in the remaining 34 patients (21%). The rate of complete necrosis according to the HCC size class was: 69%, 69%, 52%, 68%, 50% and, 13% for lesions of ⩽ 2.0, 2.1-3.0, 3.1-4.0, 4.1-5.0, 5.1-6.0, and > 6.0 cm, respectively. Kaplan-Mayer survival at 24-mo was 88%, 68%, 59%, 59%, 45%, and 53% for lesions of ⩽ 2.0, 2.1-3.0, 3.1-4.0, 4.1-5.0, 5.1-6.0, and > 6.0 cm, respectively.

CONCLUSION: Our study showed that in cirrhotic patients with single HCC smaller than 6.0 cm, TAE/TACE produces complete local control of tumor in a significant proportion of patients. TAE/TACE is an effective therapeutic option in patients with single HCC not suitable for surgical resection or percutaneous ablation therapies. Further studies should investigate if the new available embolization agents or drug eluting beads may improve the effect on tumor necrosis.

Key words: Transcatheter embolization/chemoembolization; Hepatocellular carcinoma

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INTRODUCTION

The intra-arterial treatment using transarterial chemoembolization (TACE), transarterial oily chemoembolization (TOCE) and transarterial embolization (TAE) is considered a palliative therapy for multifocal HCC not suitable for surgical resection or percutaneous ablation therapies[1-3]. Recent meta-analysis showed an improvement of overall survival in patients with well preserved liver function treated with intra-arterial treatment[4,5]. The efficacy of intra-arterial treatment in patients with single HCC is not well defined. The aim of this study was to evaluate the efficacy of intra-arterial therapy in a large series of cirrhotic patients with single HCC.

MATERIALS AND METHODS

This study is a retrospective cohort study based on the analysis of 176 consecutive cirrhotic patients with single HCC, treated with intra-arterial therapy and evaluated with

follow-up imaging at a single transplant centre. One hundred and sixty-two patients had at least one image examination (helical CT scan or triphasic contrast-enhanced MRI) after treatment and were included into the study. Diagnosis of HCC was based on radiological findings, alfa-fetoprotein level and biopsy according to the Barcelona criteria[6]. The mean age (range) of patients were 62 (35-80) years, male to female ratio was 117/45, the Child-Pugg score (mean ± SD) was 6.1 ± 1.1, MELD score (mean ± SD) was 8.7 ± 2.3, Mean diameter of HCC was 3.6 (1.0-12) cm, number of HCC in the right lobe/left lobe was 133/29.

Informed consent was not specifically required for the study, although written informed consent was obtained for every diagnostic and interventional radiology procedure.

Intra-arterial treatment was performed in patients with single non-resectable HCC and contraindications to radiofrequency thermal ablation (RFA). In our centre, contraindications to RFA are the: (1) size of the lesion that is greater than 4 cm, (2) lesion near to vital organs as gallbladder, stomach, and colon, (3) lesion adjacent to a big portal or hepatic vein branches at risk of bleeding, (4) subphrenic lesion not easily accessible for RFA and (5) lesion in subcapsular position at high risk of tumor seeding[7].

Inclusion criteria for intra-arterial treatments of HCC are as follows: Absence of extrahepatic tumor; HCC < 50% of hepatic volume; absence of complete thrombosis of main portal vein; transaminases < 300 U/L, serum bilirubin < 0.3 mg/L; serum creatinine < 0.18 mg/L; white blood cell > $2.5 \times 10^3/\mu L$; platelets > $35 \times 10^3/\mu L$; no refractory ascites; performance status < 3.

Exclusion criteria for intra-arterial treatments of HCC are as follows: extrahepatic tumor spread; ascites not controlled by diuretics; encephalopathy; active or recent (4 wk) gastrointestinal bleeding; biliary obstruction; severe debilitation; active infection or sepsis; pregnancy; failure (ejection fraction less than 50%); severe pulmonary dysfunction; serum creatinine > 0.2 mg/L; serum bilirubin > 0.3 mg/L; Hb level < 8 g/dL; White blood cells < $2.5 \times 10^3/\mu L$; platelets < $35 \times 10^5/\mu L$.

The intra-arterial treatments were performed by two radiologists with 15 and 5 years of experience in interventional radiology, respectively. TACE was performed using Epirubicine at a dose of 50 mg/m^2 of body surface; the dose was reduced to 50% if serum bilirubin level was > 0.12 mg/L and < 0.2 mg/L and/or white blood cell count (WBC) was 3-4 × $10^3/\mu L$; a dose reduction to 25% was performed if bilirubin was > 0.2 mg/L and/or WBC 2.5-3 × $10^3/\mu L$. Epirubicine was prepared in sterile drip and infused over 30 min using a peristaltic pump. Afterwards, the embolization was performed using Gelfoam (Pfitzer, Belgium) till a stagnation flow was visualized at the fluoroscopy. In patients with good liver function and superselective catherization of the hepatic artery, 2-10 mL of Lipiodol (Lipiodol Ultrafluid, Guebert, Italy) were infused, by hand, before the Gelfoam embolization (TOCE). No chemotherapeutic agent (TAE) was used in presence of WBC less than 2.5 × $10^3/\mu L$, previous episodes of neutropenia (< 500/mL), positive HBsAg and HBV DNA[8] and ejection fraction ⩽ 45%. In these patients the treatment was performed using Lipiodol and/or Gelfoam. Superselective catheterization of the artery supplying the lesion was performed whenever possible. In the other cases the treatment was performed in the branch of the right hepatic artery or in the branch of the left hepatic artery supplying the lesion. Discharge from the hospital was the day after the procedure. The intra-arterial treatment was repeated every 6-12 wk according to the tumor response based on the CT follow-up imaging and on clinical assessment.

All CT scan studies were performed with a 16-slice multidetector CT (Light speed, General Electric Medical Systems, USA) 4-6 wk after the intra-arterial treatment. Images of the liver were acquired in cranium-caudal direction, during a single breath-hold acquisition, with slice thickness 1.25 mm, collimation 2.5 mm and table speed 7.5 mm per gantry rotation. Quadruple-phases protocol was used (unenhanced phase, arterial phase, portal venous phase and late phase). Iopromide (Ultravist 370 mg I/L, Schering, Germany) contrast was injected, using a power injector (Stellant 2, Medrad) with a dose of 1.8 mL/kg of body weight at a rate of 5 mL/s. If the serum creatinine was > 0.15 mg/L, Iodixanolo (Visipaque 320 mg I/L, Amersham Healt, Italy) was used as contrast medium. Before the study, patients received 500 mL of water as oral contrast agent. The test bolus technique (10 mL of contrast material at 5 mL/s) was used to calculate the correct time of the arterial phase. Arterial scanning was performed with a delay of 8 s from the peak time of the aortic enhancement obtained at the celiac axis level. The portal venous phase and late phase acquisitions were performed after 60 s and 180 s from the beginning of contrast injection, respectively. Imaging analysis was performed by three radiologists experienced in liver imaging. The presence of arterial enhancement at the CT imaging was considered as viable tumor. In patients that underwent TOCE, the complete necrosis was considered only if the lesion had homogeneous Lipiodol uptake without contrast enhancement in arterial phase. In case of an unclear result, MRI studies with gadobenate dimeglumine (Gd-BOPTA), using a 1.5T MR Scan (General Electric Medical Systems, USA) was performed. The efficacy of intra-arterial treatment was defined according to the amount of tumor necrosis valuable on CT follow-up imaging and following the WHO recommendations[9]: complete response was defined the absence of any contrast enhancement in arterial phase, massive response as a necrosis involving 90%-99% of the lesion, partial response as a necrosis involving 50%-89% of the lesion, and poor response as a necrosis involving less than 50% of the lesion.

Patients were followed up monthly in outpatient clinics. We considered a complication due to the treatment if it occurred within 6 wk from TAE/TACE.

Statistical analysis

All analyses were performed with SPSS program. The results are expressed as mean ± SD. Survival curves were modeled using the Kaplan-Meier method.

Table 1 Rate of complete tumor necrosis according to the size of HCC

Size of HCC (cm)	*n*	Complete necrosis (% of patients)	Number of treatments (mean ± SD)
≤ 2.0	51	69	2.0 ± 1.5
2.1-3.0	35	69	2.2 ± 1.7
3.1-4.0	29	52	2.7 ± 2.0
4.1-5.0	22	68	2.8 ± 1.6
5.1-6.0	11	50	2.0 ± 1.3
> 6.0	14	13	3.3 ± 2.1

Table 2 Kaplan-Meier survival analysis according to the size of HCC

Size of HCC (cm)	12 mo survival (%)	24 mo survival (%)	36 mo survival (%)
≤ 2.0	87	87	79
2.1-3.0	85	67	54
3.1-4.0	72	58	50
4.1-5.0	88	59	49
5.1-6.0	78	45	30
> 6.0	77	53	26

RESULTS

Patients received a total of 368 sessions of TAE/TACE. The mean number of treatment sessions was 2.4 ± 1.7 per patient, range 1-9. In 69 (43%) of 162 patients a single procedure was sufficient to induce a complete tumor necrosis. Technical success was achieved in all the TAE/TACE performed. No major, life-threatening complications occurred without any perioperative mortality. As minor, reversible, complications 3 (1.8%) of 162 patients had transitory neutropenia ($< 0.5 \times 10^3/\mu L$), 2 (1.2%) of 162 patients had partial dissection of intrahepatic artery and 4 (2.4%) of 162 patients had a transitory liver failure (defined as occurrence of encephalopathy, ascites, increased bilirubin level and/or coagulopaty). The results of treatments on HCC necrosis are summarized in Table 1. On imaging analysis overall complete necrosis was obtained in 94 lesions (58%), massive necrosis was obtained in 16 lesions (10%), partial necrosis was obtained in 18 lesions (11%), and poor necrosis was obtained in the remaining 34 lesions (21%). According to the size of HCC complete necrosis was obtained in 69% of lesions ≤ 2.0 cm, 69% of lesions between 2.1-3.0 cm, 52% of lesions between 3.1-4.0 cm, 68% of lesions between 4.1-5.0 cm, 50% in lesions between 5.1-6.0 cm and 13% in lesions > 6 cm. The cumulative survival rates were 81%, 61% and 48% at 12, 24 and 36 mo respectively. Table 2 shows Kaplan-Meier survival analysis according to the size of HCC. The survival rates at 12, 24 and 36 mo were respectively: 87%, 87% and 79% for lesions ≤ 2.0 cm, 85%, 67% and 54% for lesions between 2.1-3.0 cm, 72%, 58% and 50% for lesions between 3.1-4.0 cm, 88%, 59% and 49% for lesions between 4.1-5.0 cm, 78%, 45% and 30% for lesions between 5.1-6.0 cm, 77%, 53% and 26% for lesions > 6 cm.

DISCUSSION

HCC is the fifth most common cancer worldwide. Surgical therapy, as a curative option, is indicated only in patients with single HCC without portal hypertension and preserved liver function[1]. Hepatic resection of HCC in patients with cirrhosis is associated with significant perioperative mortality and morbidity[10,11]. Cirrhotic patients with non-resectable HCC have a poor prognosis influenced by hepatic reserve function and tumor staging. TAE/TACE are the most used treatment for HCC, which are non-resectable or that can not be treated with percutaneous interventions, with proven improvement on survival in selected patient with well preserved liver function[4,5] Progression of HCC is related to neoangiogenic activity. Rationale for intra-arterial treatments for HCC is the almost complete arterial blood supply of the tumor (90%-100%) compared to normal liver parenchyma where the arterial flow is only 25% and the portal flow is responsible of the 75% of the inflow[12]. The goal of TAE/TACE is to deliver a high dose of chemotherapeutic drug and/or embolizing agent in the HCC, causing tumor necrosis and tumor control, preserving as much normal liver parenchyma. TAE/TACE is considered a palliative therapy for multifocal HCC but the efficacy in patients with single HCC is not well defined. It has been reported by Liem *et al*[13] that morbidity, mortality and short-term and intermediate-term survival data after TACE for HCC eligible for radiofrequency ablation are comparable to those reported after radiofrequency ablation in literature. In our series of patients, in 94 patients (58%) a complete necrosis was achieved. Interestingly, According to the lesion size, complete necrosis was achieved in 68% of patients with lesion between 4.1-5.0 cm and in 50% of patients with lesion between 5.1-6.0 cm, a very poor rate of complete response, 13%, was obtained in lesions > 6 cm. Livraghi *et al*[14] report a complete necrosis after radiofrequency ablation, detected by computed tomography follow-up, in 71% of cases with non-infiltrating HCC between 3.1-5.0 cm in diameter and in 25% of lesions > 5 cm. Cabassa *et al*[15] report a complete necrosis after radiofrequency ablation, detected by computed tomography follow-up, in 53% of lesions between 3.1-5.0 cm and in 20% of lesions > 5 cm. Our results after TAE/TACE in medium size, single, HCC in causing tumor necrosis are comparable to data reported after radiofrequency ablation, in same size lesions, by Livraghi and Cabassa.

Our data on survival are similar to data reported by Takayasu *et al*[16] in a recent large, prospective, cohort study of transarterial chemoembolization for non-resectable HCC, the cumulative survival rate of 3648 patients with single HCC was 87% at one year and 57% at 3 years; according to tumor size the survival reported was 83% at one year and 43% at 3 years for lesions between 3.0-5.0 cm and 63% at one year and 30% at 3 years for lesions > 5 cm. Our data on overall survival rate are also comparable with data reported by Teh *et al*[10] who reports an overall survival rate of patients with cirrhosis undergoing hepatic resection of 50% at 3 years but with a reported perioperative mortality of 16%. In a recent paper of

Benzoni *et al*[11], 7% of perioperative mortality and 47% of postoperative morbidity (including the rising of ascites, hepatic insufficiency, biliary fistulas, hepatic abscess, hemoperitoneum and pleural effusion) is reported after hepatic resection for HCC in cirrhotic patients.

The absence of major complication and the low rate of minor complication of our study could be explained by an accurate clinical patients' selection. In fact no patient with Child Pugg class C was treated. The use of segmental or subsegmental treatments is in our opinion mandatory, limiting the injury to the surrounding non-tumoral parenchyma and reducing the adverse effects of single or repeated intra-arterial treatments on liver function as reported in previous studies[17,18]. At the same time the systematic use of micro-catheters to selectively catheterize the feeding artery of the lesion increases the amount of chemotherapeutic drug and/or of embolizing agents in the target HCC increasing the amount of necrosis. Super selective treatment should be recommended especially in patients with Child Pugg class B or MELD score $\geqslant 9$.

The use and dosage of Epirubicine not with a fixed dose but according to patients' body surface, severity of liver disease and white blood cells count could have an important rule in the low incidence of complications reported. All Patients received antibiotic prophylaxis before TAE/TACE and no cases of sepsis or hepatic abscesses happened in the follow up. Patients were well hydrated before and after procedure to avoid renal injuries. If creatinine was > 0.15 mg/L, a less nephrotoxic contrast dye was used for intra-arterial treatments and for CT scan and no cases of renal impairment were recorded.

The use of more efficient chemotherapeutic drug and embolizing agents, associated with systematic selective catheterization of the feeding artery with micro-catheter, could further improve our results. As limitation of our study we did not analyze the relationship between the dosage of chemotherapeutic drug used and the dose of the Lipiodol used with the tumoral necrosis and the survival rate obtained because in our protocol the dosages of Epirubicine and Lipiodol used were not fixed, but dependent on clinical characteristic of the patient the same day of the procedure, so in the same patient it was possible to have different dosages of chemotherapeutic drug and Lipiodol in repeated treatments.

In conclusion our study showed that in cirrhotic patients with single HCC $\leqslant$ 6 cm, TAE/TACE can be considerate a safe and effective therapeutic option producing complete local control of tumor in a significant proportion of patients. In single HCC between 3 and 5 cm the effect on necrosis induced by intra-arterial treatments is not different from the data reported using RFA. Accurate patients' selection and factors procedure-related (use of micro-catheters, selective treatments, sterile drip for cytotoxic drug and antibiotic prophylaxis) reduce the possible complications increasing tumor necrosis. At our opinion an important aspect is the needs to standardize the dose of cytotoxic drug on the basis of the clinical characteristics of the patients to avoid liver failure.

Further studies should investigate if the new available embolization agents or drug eluting beads may improve the effect on tumor necrosis.

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