

RAPID COMMUNICATION

Predictive factors of tumor response to trans-catheter treatment in cirrhotic patients with hepatocellular carcinoma: A multivariate analysis of pre-treatment findings

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Abstract

AIM: To elucidate the pre-treatment clinical and imaging findings affecting the tumor response to the transcatheter treatment of unresectable hepatocellular carcinoma (HCC).

METHODS: Two hundred cirrhotic patients with HCC received a total of 425 transcatheter treatments. The tumor response was evaluated by helical CT and a massive necrosis (MN) was defined as a necrosis > 90%. Twenty-five clinical and imaging variables were analyzed: uninodular/multinodular HCC, unilobar/bilobar, tumor capsula, hypervascular lesion, portal vein thrombosis, portal hypertension, ascites, platelets count, aspartate transaminases/alanine transaminases (AST/ALT), alfa-fetoprotein (AFP) > 100, AFP > 400, serum creatinine, virus hepatitis C (VHC) cirrhosis, performance status, age, Okuda stage, Child-Pugg stage, sex, CLIP (Cancer of the Liver Italian Program) score, serum bilirubin, constitutional syndrome, serum albumine, prothrombin activity, BCLC (Barcelona Clinic Liver Cancer) stage. Prognostic factors of response were subjected to univariate analysis and thereafter, when significant, to the multivariate analyses.

RESULTS: On imaging analysis, complete response was

obtained in 60 (30%) patients, necrosis > 90% in 38 (19%) patients, necrosis > 50% in 44 (22%) patients, and necrosis < 50% in 58 (29%) patients. Ninety-eight (49%) of the 200 patients were considered to have a MN. In univariate analysis, significant variables ($P < 0.01$) were: uninodular tumor, unilobar, tumor size 2-6 cm, CLIP score < 2, absence of constitutional syndrome, and BCLC stage < 2. In a multivariate analysis, the variables reaching statistical significance were: presence of tumor capsule ($P < 0.0001$), tumor size 2-6 cm ($P < 0.03$), CLIP score < 2 ($P < 0.006$), and absence of constitutional syndrome ($P < 0.03$). Kaplan-Mayer cumulative survival at 12 mo was 80% at 24 mo was 56%. MN was associated with a longer survival ($P < 0.0001$).

CONCLUSION: MN after transcatheter treatment is more common in the presence of tumor capsule, maximum diameter of the main lesion between 2 and 6 cm, CLIP score < 2 and absence of constitutional syndrome. The ability to predict which patients will respond to transcatheter treatment may be useful in the clinical decision-making process, and in stratifying the randomization of patients in clinical trials.

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Key words: Hepatocellular carcinoma; Trans-catheter embolization/chemoembolization; Tumor response

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INTRODUCTION

Trans-catheter treatment is extensively used to treat hepatocellular carcinoma (HCC) not suitable for surgical resection or percutaneous ablation therapies. Transarterial chemoembolization (TACE), transarterial oily chemoembolization (TOCE) and transarterial embolization

(TAE) have been adopted^[1-8]. Prognosis of patients with HCC complicated with cirrhosis mainly depends on the tumor growth, progression of the underlying liver disease, and effectiveness of anti-tumor treatment. Recent meta-analysis showed that the overall survival of patients with well preserved liver function was improved after intra-arterial treatment^[9,10]. The primary goal of the trans-catheter treatment is to achieve a massive necrosis, to reduce tumor size, and prevent its dissemination and portal vein invasion. Unfortunately, the tumor response to trans-catheter treatment is heterogeneous with a wide range of necrosis that cannot be accurately predicted. The lack of well-defined prognostic indicators inspired us to perform the present study to analyze the tumor response and the pre-treatment imaging and clinical prognostic factors predictive of response in patients with HCC and compensated cirrhosis who were treated by trans-catheter treatment.

MATERIALS AND METHODS

This is a retrospective cohort study based on the analysis of 200 consecutive cirrhotic patients with single or multifocal HCC, treated with intra-arterial therapy and evaluated with follow-up imaging at a single transplant centre. Patients who had at least one image examination (16-slides helical CT scan or triphasic contrast-enhanced MRI) before and after treatment were included into the study. Diagnosis of HCC was based on radiological findings, alfa-fetoprotein level and biopsy according to the Barcelona criteria^[11]. Bone metastases were ruled out by bone scintigraphy; lung and abdominal metastases were ruled out by CT scan. Liver function impairment was estimated with routine biochemical parameters reflecting liver function. The cardiac risk was evaluated by EKG and left ventricular ejection fraction (LVEF), as measured by multi-gated angiography scan (MUGA scan) or echocardiography. HCC and patient's characteristics at admission are reported in Table 1. Informed consent was not specifically required for the study, although written informed consent was obtained for each diagnostic and interventional radiology procedure.

All CT scan studies were performed with a 16-slice multidetector CT (Light speed, General Electric Medical Systems, USA) before and 4-6 wk after the intra-arterial treatment. Quadruple-phases protocol was used (unenhanced phase, arterial phase, portal venous phase and late phase).

All CT images were evaluated by at least 2 radiologists. Pre-treatment studies were analyzed without knowledge of the final outcomes of the patients. A consensus of the readers was reached in all cases. The following CT features were evaluated: number of lesions (single, multiple), size of the main lesion (maximum diameter), hepatic distribution (unilobar or bilobar), tumor extension (≤ 3 lesions each ≤ 3 cm or > 3 lesions or one > 3 cm), vascularity of the lesions (hypervascular, hypovascular), tumor capsule, portal vein invasion (lobar, segmental, or subsegmental), signs of portal hypertension (spontaneous splenorenal shunt, patency of umbelical vein, patency of coronary vein), ascites, and necrosis. In post-treatment

Table 1 Patient and HCC characteristics at admission

Age (mean \pm SD, range)	63 \pm 8.62 (35-81)
Sex distribution (male/female)	138/62
Liver cirrhosis etiology:	
Hepatitis C	158
Hepatitis B	29
Others	13
Child Pugh score A/B/C	136/59/5
Clip score (0/1/2/3/4/5)	53/79/52/11/4/1
BCLC stage (1/2/3/4)	61/115/14/0
Constitutional syndrome (yes/no)	22/178
Performance status (0/1/2/3)	177/14/8/1
HCC uninodular/multinodular	96/104
HCC unilobar/bilobar	148/52
Tumor capsula: yes/no	83/114
Portal vein thrombosis:	
absent/partial/complete	185/15/0
Alfa-fetoprotein:	83/48/69
< 20/20-100/> 100 ng/mL	

studies, the presence of arterial enhancement at CT imaging was considered as viable tumor. In patients who underwent TOCE, the complete necrosis was considered only if the lesion had homogeneous Lipiodol uptake without contrast enhancement in arterial phase. In case without clear results, MRI 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 and/or MR follow-up imaging and the WHO recommendations^[12]. The presence of non-enhanced tumor areas was defined as tissue necrosis and expressed as percent of the total tumor volume. Tumor necrosis was considered complete when no foci of enhancement were seen within the tumor or at its periphery. In patients with multiple lesions, the necrosis was computed as average of tumor necrosis in each lesion. The response to treatment was classified as: complete response, necrosis $> 90\%$, necrosis $> 50\%$, and necrosis $< 50\%$. In this study, a tumor necrosis $> 90\%$ over the treatment interval was classified as massive necrosis (MN).

Intra-arterial treatment was performed in patients with multifocal HCC or single unresectable HCC and contraindications to radiofrequency thermal ablation (RFA).

In our centre, contraindications to RFA are: size of the lesion greater than 4 cm, lesion near to vital organs such as gallbladder, stomach, and colon, lesion adjacent to a big portal or hepatic vein branches at risk of bleeding, subphrenic lesion not easily accessible for RFA and lesion in subcapsular position at high risk of tumor seeding^[13].

Exclusion criteria for intra-arterial treatment were HCC volume $> 50\%$ of total hepatic volume, complete thrombosis of main portal vein, AST/ALT > 300 U/L, serum bilirubin > 3 mg/dL, serum creatinine > 1.8 mg/dL, white blood cell (WBC) $< 2.5 \times 10^3/\mu\text{L}$, platelets $< 35 \times 10^3/\mu\text{L}$, severe ascites and performance status > 3 .

TACE was performed using Epirubicine at a dose of 50 mg/m² of body surface; the dose was reduced to 50% if serum bilirubin level was > 1.2 mg/dL and < 2 mg/dL and/or white blood cell count (WBC) was $34 \times 10^3/\mu\text{L}$;

a dose reduction to 25% was administered if bilirubin was > 2 mg/dL and/or WBC $2.53 \times 10^3/\mu\text{L}$. Epirubicine was prepared in sterile drip and infused over 30 min using a peristaltic pump. Afterwards, the embolization was performed using Gelfoam (Pfizer, Belgium) till a stagnation flow was visualized at the fluoroscopy. In patients with acceptable liver function and superselective catheterization of the hepatic artery, 2-10 mL of Lipiodol (Lipiodol Ultrafluid, Guebert, Italy) was infused before the gelfoam embolization (TOCE)^[14]. No chemotherapeutic agent (TAE) was used in the presence of WBC less than $2.5 \times 10^3/\mu\text{L}$, previous episodes of neutropenia ($< 500/\text{mL}$), positive HBsAg and HBV DNA^[15] and ejection fraction $\leq 45\%$. These patients were treated with lipiodol and/or gelfoam. In patients with single HCC, superselective catheterization of the artery supplying the lesion was performed whenever possible, in the other cases the treatment was given in the branch of the right hepatic artery or in the branch of the left hepatic artery supplying the lesion. In patients with multifocal HCC, treatments were given in the right hepatic artery (RHA) or in the left hepatic artery (LHA). In case of multifocal, bilobar HCC, no treatment was given in RHA and LHA during the same session. After the treatment, the patients were carefully observed in a conventional hospitalization room, and analgesics were administered if necessary. Oral intake was reinitiated as soon as possible according to the tolerance of the patients. Usually the day after the procedure, after confirming the absence of clinical abnormalities, the patients were discharged and followed up in the outpatient clinic.

The intra-arterial treatment was repeated every 6-12 wk according to the tumor response based on the follow-up imaging and clinical assessment.

Statistical analysis

Twenty-five clinical and imaging variables were analyzed, including uninodular/multinodular HCC, unilobar/bilobar, tumor capsula, heparvascular lesion, portal vein thrombosis, portal hypertension, ascites, platelets count, AST/ALT, AFP > 100 , AFP > 400 , serum creatinine, VHC cirrhosis, performance status, age, Okuda stage, Child-Pugg stage, sex, CLIP score, serum bilirubin, constitutional syndrome, serum albumine, prothrombin activity, BCLC stage.

The relationship between these variables and the tumor response was first assessed by univariate analysis using the Chi-square test or Student's *t* test when indicated. For qualitative variables, patients were grouped according to the presence or absence of each variable. For quantitative variables, the cut-off level was determined evaluating the relationship between the sensitivity and the specificity of the MN at different cut-off points from a ROC curve. To identify independent predictors of MN occurrence, all the variables reaching statistical significance in the univariate analysis were subsequently included in a multivariate analysis using the step-wise logistic regression procedure. A *P* value of less than 0.05 was considered significant. Statistical analyses were performed with the SPSS software (SPSS Institute Inc., Cary, NC). Survival curves were modelled using the Kaplan-Meier method.

RESULTS

Patients received a total of 425 sessions of intra-arterial treatments. The mean number of treatment sessions was 2.1 ± 2.0 per patient, range 1-8. Interval of treatment was 76 ± 48 d (range 16-249 d). Type of treatments performed were: TACE 243 (57%), TOCE 126 (30%) and TAE 56 (13%). Technical success was achieved in all the treatments performed. No major life-threatening complications occurred.

On imaging analysis, complete response was obtained in 60 (30%) patients, necrosis $> 90\%$ in 38 (19%) patients, necrosis $> 50\%$ in 44 (22%) patients, and necrosis $< 50\%$ in 58 (29%) patients. In this analysis, 98 (49%) of the 200 patients were considered to have MN. At univariate analysis, significant variables ($P < 0.01$) were: uninodular tumor, unilobar, tumor size 2-6 cm, CLIP score < 2 , absence of constitutional syndrome, and BCLC stage < 2 . In a multivariate analysis, the variables reaching statistical significance were: presence of tumor capsule (β -coefficient 1.447, $P < 0.0001$), tumor size 2-6 cm (β -coefficient 0.838, $P < 0.03$), CLIP score < 2 (β -coefficient 1.074, $P < 0.006$), and absence of constitutional syndrome (β -coefficient 1.764, $P < 0.03$). Kaplan-Meier cumulative survival was 80% at 12 mo and 56% at 24 mo. The survival of patients with and without MN was 95% and 75% at 12 mo, and 70% and 55% at 24 mo, respectively. Massive tumor necrosis was associated with a longer survival ($P < 0.0001$).

DISCUSSION

Transcatheter treatment is the most common choice for patients with surgically unresectable HCC and contraindications to percutaneous treatment such as PEI, and RF thermal ablation. The arterial embolization with or without chemotherapy induces tumor necrosis by occlusion of the feeding artery of the HCC, and its clinical efficacy has been documented^[3,4,16-21]. 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 as possible. The imaging and clinical factors affecting the tumor response after transcatheter treatment remain to be elucidated. The aim of this study was to identify, by means of multivariate analyses, the pre-treatment variables of independent predictive value of MN in patients with cirrhosis managed with transcatheter therapy.

Our multivariate analysis showed that two tumor-related factors such as tumor capsule and maximum diameter of the main tumor are the only independent factors significantly affecting the tumor response to the transcatheter treatment. The presence of a well-recognizable tumor capsule at the pretreatment CT scan was the most important independent predictive factor of MN after transcatheter treatment. According to our results, previous pathological studies performed on liver resection following transarterial chemoembolization^[22,23] demonstrated that encapsulated HCCs are more responsive to the transcatheter treatment than non-encapsulated tumors. Interestingly, a significant correlation

between the thickness of the capsule and the effectiveness of tumor necrosis after chemoembolization has also been documented^[24,25]. The reason for the relatively poor necrosis of tumors without capsule is not clear. Wasaka *et al* showed that barium sulfate infused into the portal vein entered into the non-encapsulated tumors but not into encapsulated tumors, suggesting that there is a difference in the type of blood supply that may greatly influence the tumor necrosis after embolization of the feeding hepatic artery^[23]. The type of histologic growth pattern at the tumor-nontumor boundary may also affect the necrosis occurrence after transcatheter treatment. HCC is usually the expanding type in encapsulated tumors and replacing type in unencapsulated tumors and chemoembolization appears to be most efficacious for HCC with growth expanding pattern. The poor results expected in the replacing type of HCC may be related to the fact that in the case of tumor, cells replace hepatocytes, the blood spaces communicate with sinusoids supplied by portal blood flow^[26,27]. A limitation of the pathological studies is that they were performed weeks or months after the chemoembolization, and the granulated tissue between HCC and normal liver parenchyma, secondary to the treatment response, could simulate a true capsule. In this case, the pseudocapsule could be an indicator and not a predictor of tumor response^[28]. Our results showed that the naturally formed capsule of encapsulated HCC resulting from condensed reticulin fibers produced by atrophic changes of noncancerous liver tissue and detected at the pretreatment CT scan, is the most important independent predictive factor to obtain MN after transcatheter treatment. However, the capsule seems to form when the tumors are small, and larger tumors are commonly unencapsulated. Finally, in absence of a very well-defined capsule, one must keep in mind the possibility that a negative CT image may not completely exclude the presence of capsule and may give partial information about its integrity. It is known the CT scan is limited in detecting capsular invasion of tumor cells, small satellite nodules, and tumor thrombi of the peripheral portal vein branches that are rather poorly responsive to the transcatheter treatment probably because they receive blood supply from the portal vein^[23-25,28].

We obtained MN after transcatheter treatment more frequently in nodules with a maximum diameter of 2-6 cm. Similarly, a previous histologic study evaluating the effect of chemoembolization showed that it is effective for encapsulated HCC measuring between 2.3 and 5.5 cm in diameter^[25]. TAE is usually less effective for HCC smaller than 2 cm in diameter^[27,29]. The reason for the failure of a complete necrosis of the small tumors is not clear. No significant difference of the predominant lesion vascular pattern was found in this study between patients with or without MN. The apparent discrepancy from previously reported studies^[30] might be due to the fact that in our series the hypovascular pattern was very uncommon.

A CLIP score < 2 and the absence of constitutional syndrome are strong independent clinical predictors of MN after transcatheter treatment because these kind of patients have a preserved liver function and multiple treatments might yield a good response.

In conclusion, pretreatment helical CT and clinical findings provide accurate prediction of tumor response in patients with HCC and compensated cirrhosis. The MN (> 90%) is more common in the presence of capsule, maximum diameter of 2-6 cm and in well compensated patients with CLIP score of 1 and without constitutional syndrome. The ability to predict which patients will respond to transcatheter treatment may be useful in the clinical decision-making process, and in stratifying the randomization of patients in the therapeutic clinical trials. The prognostic implications and the survival of patients with massive tumor necrosis require further studies.

COMMENTS

Background

Trans-catheter treatment is extensively used to treat hepatocellular carcinoma in cirrhotic patients to achieve a massive necrosis, to reduce tumor size, and prevent its dissemination and portal vein invasion. Tumor response after trans-catheter treatment cannot be accurately predicted.

Research frontiers

The aim of this study is to analyze tumor response and the pre-treatment imaging and clinical prognostic factors predictive of response in patients with HCC and compensated cirrhosis who were managed by trans-catheter treatment.

Innovations and breakthroughs

This study clearly showed that massive necrosis is more common in presence of capsule, a maximum diameter of 2-6 cm and in well compensated patients with CLIP score of 1 and without constitutional syndrome.

Applications

The ability to predict which patients will respond to transcatheter treatment may be useful in the clinical decision-making process and in stratifying the randomization of patients in clinical trials.

Terminology

CLIP (Cancer of the Liver Italian Program) prognostic score includes Child-Pugh stage, tumor morphology and extension, serum alpha-fetoprotein (AFP) levels, and portal vein thrombosis. Constitutional syndrome is characterized by weight loss, malaise and anorexia.

Peer review

This is an interesting study, aiming at identifying the factors predicting tumor response to the trans-catheter treatment in cirrhotic patients with HCC. The authors concluded that presence of tumor capsule, a maximum diameter between 2 and 6 cm, CLIP score < 2 and absence of constitutional syndrome were independent predictors of massive necrosis. The study is well conducted. The results are clearly reported and support the main conclusions.

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