

TACE Combined with PSE in Treating Hepatocellular Carcinoma with Hypersplenism

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OBJECTIVE To observe the effectiveness and safety of transcatheter arterial chemoembolization (TACE) combined with partial splenic embolization (PSE) in treating primary hepatocellular carcinoma (HCC) with hypersplenism.

METHODS Thirty HCC patients with liver cirrhosis, portal hypertension and hypersplenism were treated with TACE and PSE. The degree of tumor volume reduction and remission of hypersplenism were observed.

RESULTS The tumor reduction rate of the HCC was 73.3%. Twenty-eight patients had hypersplenic remission with a rate of 93.3%. There were no severe complications such as hepatic abscesses.

CONCLUSION TACE combined with PSE is a safe and effective method to treat HCC with liver cirrhosis, portal hypertension and hypersplenism.

KEYWORDS: hepatocellular carcinoma, transcatheter arterial chemoembolization, partial splenic embolization, hypersplenism.

Primary hepatic carcinoma (HCC) is one of the most common and lethal cancers in China with an increasing mortality.^[1] Moreover, only 10% of newly diagnosed HCC patients are candidates for an operation. Transcatheter arterial chemoembolization (TACE) is currently considered to be the optimal therapy in treating advanced-stage HCC patients,^[2,3] but over 70% to 90% of HCC patients have the complication of cirrhosis or hypersplenism. Following TACE treatment leukocytes return to normal, which prolonged the intermission time for retreatment. Hepatic arterial chemoembolization after partial splenic embolization (PSE) has been used to treat 30 HCC patients complicated with cirrhosis, portal hypertension and hypersplenism in our department from October 1999 to November 2002 with satisfactory results.

MATERIALS AND METHODS

Clinical data

There were 30 patients with HCC involved in this research (26 male, 4 female, ages from 31 to 67 years with an average of 49 years). All the patients received interventional operations from 2 or 6 times with an average of 3.5 times. Tumor markers, digital subtraction angiography,

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ultrasound, computed tomography or MRI were performed in all cases. The results were consistent with the Diagnostic Criteria for HCC made by the Society of Liver Cancer, Chinese Anti-Cancer Association (CACA) in 1999. Digital subtraction angiography showed new tumor vessels and tumor stain in all cases. Three cases had tumor diameters of less than 5 cm, 16 cases were more than 10 cm, 11 cases varied from 6 to 10 cm. All were nodule type with isolated nodules in 13 cases and multiple nodules in 17 cases. Four cases had an embolus in the branch of the portal vein. Based on the TNM staging of liver cancer made by the UICC,^[4] 11 cases were in Stage II, 13 cases were in Stage IIIa and 6 cases were in Stage IIIb. Nine cases of liver function were Child A according to Child-Pugh Grading, 18 cases were Child B and 3 cases were in Child C.

All patients had complications of portal hypertension, splenomegaly and hypersplenism. The peripheral white blood cells numbered from $1.5 \times 10^9/L$ to $3.8 \times 10^9/L$, with an average of $3.1 \times 10^9/L$. Thrombocytes varied from $45 \times 10^9/L$ to $76 \times 10^9/L$ with an average of $64 \times 10^9/L$. Two cases had a history of hematemesis.

Methods

Hepatic artery chemoembolization (TACE)

A catheter was placed in the celiac artery through a femoral arteriopuncture by Seldinger's technique. Hepatic angiography was performed to identify the size, position, type of tumor, presentation of arteriovenous fistula and condition of the major artery. Following superselection of the major artery for tumor and chemotherapeutic perfusions (fluorouridine 750~1000 mg, hydroxycamptothecin 10~20 mg, cisplatin 60~100 mg) were performed. After the mixture of chemotherapeutics and lipiodol (adriamycin or epirubicin 60~80 mg mitomycin 10~20 mg mixed with lipiodol 5~20 ml) was perfused, gelatin particles were embolized in the artery. The treatments were repeated 2 to 6 times with the intervals between 4 to 6 weeks.

Partial splenic embolization (PSE)

Splenic arteriography was carried out after TACE to definite the splenic artery location and condition. Then the catheter was placed into the distal end of the pancreatic artery to avoid the possibility of pancreatitis. Gelatin sponge particles were infused under DSA. The particles had an average diameter of 1 mm with a maximum of 2 mm. The number of particles varied from 30 to 60. Thus different branches of the splenic artery could be embolized. Infusion was stopped when the blood flow in the splenic artery became slow. Antibiotics were administrated for 3 to 7 days after the operation. Peripheral blood was examined at 2 days after treatment and every week for the first month. CT scans were performed in the first and the second month after the operation to evaluate the embolized areas. If the area was less than 20%, the treatment would be repeated in the same way.

Evaluation of therapeutic effect

The Response Evaluation for Solid Tumors^[5] recommended by the WHO was utilized to evaluate the tumor diminution including complete remission (CR), partial remission (PR) and progressive disease (PD).

RESULTS

Diminution of the tumor and spleen

Results of CT scans 4 weeks after treatment showed that 16.7% of the patients had complete filling of lipiodol in their tumor and 19 cases had their tumor volumes decreased by more than 25% with a percentage of 63.3%.

When the second interventional treatment finished, tumor volumes were completely filled with lipiodol in all patients. Hepatic arteriography showed that the nourishing arteries of the tumor became thinner compared to pretreatment, tumor vessels decreased significantly and collateral circulation appeared in some of the patients.

There were 3 cases in CR, all of whom had a solitary tubercle and 19 cases in PR, 6 cases had no change and 2 cases had PD. Objective response (OR), i.e. CR+PR, was 73.3% (22/30). Infarction and liquefaction showed in the marginal zone of the spleen and in

normal splenic tissue in CT scans. The embolized area varied from 25.8% to 42.2%. The infarction size of 5 cases was more than 40%, of 23 cases more than 30% and of 2 cases less than 30%. Angiography showed that the splenic artery became thinner compared to pretreatment. The volume of the spleens in CT scans decreased 2 weeks postoperatively with the degree of decrease degree of resulting in a positive correlation with the infarction or liquefaction.

Side effects and complications

Post embolization syndrome

Stomachache, fever, nausea and vomiting appeared on the day of operation. The temperatures fluctuated from 37°C to 38°C with the highest being 39.6°C. Fevers lasted from 4 to 28 days with an average of 9 days. Pain appeared in the hepatic and splenic regions, lasting for 7 to 18 days. Antidyne was administrated in serious cases.

Fluidify

Ascities appeared in 2 cases 1 week after treatment and then vanished. No pleural effusion or pericardial effusion occurred.

Complications

No serious complications such as splenic abscess, splenic rupture, renal failure or liver function failure occurred.

Peripheral blood cells

Leukocytes and thrombocytes

Leukocytes (WBC) and thrombocytes began to return to normal 2 days after embolization. WBC amounts of all patients raised to the normal level in 1 week with an average of $5.1 \times 10^9/L$. Then WBC levels descended to $(4.0\sim 5.0) \times 10^9/L$ in 2 or 3 weeks. Thrombocytes reached a normal level in 1 or 2 weeks following embolization with an average of $140 \times 10^9/L$. WBC numbers were less than $4.0 \times 10^9/L$ again 2 weeks later in 2 cases whose embolic areas were less than 30%.

Erythrocyte

No obvious variation occurred at 1, 4 and 8 weeks.

Clinical performance

Because the tumors were depressed by TACE and hypersplenism and portal hypertension were alleviated by PSE, the quantity of life was improved significantly. Appetite and physical capacity were better compared to those of pretreatment, and body weight increased. The Karnofsky grade raised 10–20 points in 25 cases with a percentage of 83.3% of all patients. Two patients who had a history of alimentary tract hemorrhage had none after embolism. The life span of 17 patients was over 1 year, for 3 cases it was more than 2 years and for 8 cases it was more than 6 months. Two patients died of hepatic encephalopathy 6 months after interventional treatment.

DISCUSSION

TACE combination with PSE

In recent years, TACE has been applied extensively and has been regarded as the optimal non-surgical operation for treating HCC.^[6,7] But most HCC patients in China have had a background of liver cirrhosis. So splenomegaly accompanied with hypersplenism, portal hypertension and upper gastrointestinal hemorrhage are not only the main cause of death, but also result in impairment of immunological function and the quality of life. In treating HCC by TACE to increase longevity and quality of life, it is imperative to treat hypersplenism, portal hypertension and upper gastrointestinal hemorrhage caused by cirrhosis. Complications such as hypoleukemia and thrombocytopenia caused by hypersplenism can alter the therapeutic effect.

So we utilized TACE combined with PSE to treat HCC patients with hypoleukemia and thrombocytopenia which then soon normalized. TACE combined with PSE were helpful to restore immunological function, provide conditions appropriate for interventional treatment, shorten the intervals between 2 treatments and improve therapeutic effects.^[8] Moreover, with the pressure on hepatic

sinusoid decreased after TACE and PSE, portal pressures were lessened and the possibility of hemorrhage lowered to some degree.^[9]

Control of embolized area

The means to control the embolized area accurately is still a concern. To address this problem, a blood flow meter was used to control the quantity of infusion and increase the embolized area.^[10] Tang and Zhu^[11] considered that it was enough to improve hypersplenism when a 30% area was embolized. Slow blood flow in DSA has been considered to be the standard in current clinical practice, which usually has lead to over-embolization.

It is generally accepted that satisfactory results can be obtained with few complications and low recurrence rate if the embolized volume reached 50% of the spleen. Our results showed that the peripheral blood cell level returned to normal in a short time when the embolized area varied from 25.8 to 42.4%.

It is notable to avoid embolizing the main branch of the splenic artery and development of necrosis of other normal organs. It is helpful to combine an observation of blood flow in the splenic artery with quantitation of embolic-inducing agents.

In our opinion, it is safe and effective if the embolized area is less than 40%.

Side effects

Main side effects of TACE and PSE include stomachache, fever, nausea and vomiting, which can be ameliorated though general treatment. In our research, no serious complications occurred such as subphrenic abscess, splenic abscess, hemorrhage or peritonitis caused by splenic rupture.

In our opinion, TACE combined with PSE is safe and effective only when the combination of blood flow monitoring, lipiodol quantitation, broad-spectrum

antibiotic administration was given preoperatively and postoperatively and sterile technique used. Refractory ascites, an extensive tumor embolus in portal vein and a diffuse HCC are contraindications for TACE combined with PSE.

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