Perioperative safety analysis of transcatheter arterial chemoembolization for hepatocellular carcinoma patients with preprocedural leukopenia or thrombocytopenia

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Abstract. Patients with hepatocellular carcinoma (HCC) exhibit a high incidence of concomitant cirrhosis with leukopenia and/or thrombocytopenia. In the present study, perioperative changes in the white blood cell (WBC) and platelet (PLT) counts and associated complications were investigated to assess the safety of transcatheter arterial chemoembolization (TACE) for HCC patients with preprocedural leukopenia or thrombocytopenia. The records of 1,461 HCC patients who received TACE between January 2012 and December 2013 were retrospectively reviewed. The incidence of complications during the perioperative period and changes in the WBC and PLT counts were recorded. A Chi-squared test was used to evaluate the associations between postoperative infection and preprocedural WBC count and between bleeding at the puncture site and preprocedural PLT count. The WBC count of the majority of the patients increased within 3 days and returned to the preprocedural level within 30 days after TACE. The PLT count decreased within 3 days and returned to the preprocedural level within 30 days after TACE. The major complications were liver decompensation (n=66), puncture site bleeding (n=45), infection (n=33), severe thrombocytopenia (n=8), upper gastrointestinal bleeding (n=6), tumor bleeding (n=4) and agranulocytosis (n=3). A Chi-squared test revealed that postoperative infection was not associated with preprocedural WBC count and puncture site bleeding was not associated with decreased PLT count due to hypersplenism. Therefore, TACE was found to be safe for HCC patients with preprocedural thrombocytopenia or leukopenia due to hypersplenism, with a low incidence of major complications during the perioperative period.

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Abbreviations: HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; WBC, white blood cell; PLT, platelet

Key words: hepatocellular carcinoma, transcatheter arterial chemoembolization, leukopenia, thrombocytopenia

Introduction

Hepatocellular carcinoma (HCC) is the fifth-most common malignancy and the third leading cause of cancer-related mortality worldwide (1). The onset of HCC is insidious, and patients with early-stage disease usually have no symptoms or signs, making diagnosis difficult. HCC patients may also manifest with hepatitis and cirrhosis, so the non-specific clinical symptoms, such as jaundice, ascites, fatigue and abdominal pain, are often considered as the manifestations of hepatitis or cirrhosis. Thus, the majority of the patients have advanced HCC or distant metastases at diagnosis, and only 20% are eligible for surgical intervention (2). Previous studies have confirmed that transcatheter arterial chemoembolization (TACE) may delay the progression and vascular invasion of HCC, thereby prolonging patient survival. Thus, TACE has been considered to be a treatment of first choice for patients with intermediate-advanced HCC who are not suitable candidates for surgical interventions (3-5). TACE is minimally invasive, may be performed repeatedly, causes little damage to the liver in most patients, has few complications, and is associated with a short duration of hospital stay (6,7).

The main complications of TACE are liver failure, acute kidney injury, liver abscess, puncture site bleeding, bone marrow suppression and infection (8,9), all of which occur at a low incidence. HCC patients usually have pre-existing cirrhosis (10,11) and, therefore, have a high incidence of liver dysfunction and portal hypertension, conditions that may cause reductions in white blood cell (WBC) and platelet (PLT) counts. The requirements regarding WBC and PLT counts in cancer patients receiving intravenous chemotherapy are strict, and the majority of cancer patients with low WBC and PLT counts are susceptible to infection and bleeding. TACE may also lead to severe thrombocytopenia or bleeding at the puncture site in patients with mild thrombocytopenia, and infection or agranulocytosis in patients with leukopenia. Thus, the 2011 Chinese guidelines for the diagnosis and treatment of HCC (12) state that a WBC count $<3.0x10^9/l$ and a PLT count $<60x10^9/l$

are contraindications for TACE in patients with HCC. In our clinical practice, TACE is considered to be relatively safe for HCC patients with WBC or PLT counts below these thresholds, and such patients do not commonly experience severe infection, bleeding, agranulocytosis, or thrombocytopenia following TACE. Ooka *et al* (13) also performed TACE safely in HCC patients with reduced preprocedural PLT counts.

The required WBC and PLT counts for administration of TACE to HCC patients with cirrhosis differ among countries (12,14-16), with some countries not even taking WBC or PLT counts into consideration (14-16). However, the Chinese guidelines have strict requirements for WBC and PLT counts (12), which may represent a challenge for clinicians in China. The aim of the present study was to retrospectively review the cases of HCC patients with cirrhosis who received TACE between January 2012 and December 2013 and investigate the changes in WBC and PLT counts prior to and following TACE and the incidence of complications, in order to assess the safety of TACE during the perioperative period among these patients.

Patients and methods

Clinical characteristics. The medical records of HCC patients (n=1,461) with cirrhosis who received TACE at the Beijing 302 Hospital (Beijing, China) between January 2012 and December 2013 were retrospectively reviewed. Following exclusion of patients who received a splenectomy (n=104), 1,357 patients who underwent a total of 2031 TACE procedures were included (Table I). Imaging examinations or liver biopsy were performed in all the patients. HCC was diagnosed according to the 2011 Chinese guidelines for the diagnosis and treatment of HCC (12). The patients were divided into early, intermediate and advanced stage according to the Barcelona Clinic Liver Cancer (BCLC) classification system (17). The indications for TACE were i) intermediate- to advanced-stage hepatocellular carcinoma (HCC) that could not be surgically resected, without severe liver or kidney dysfunction [including non-massive HCC (<70% of the liver); multinodular HCC; incomplete obstruction of the main portal vein or formation of compensatory collateral vessels in the presence of complete obstruction of the main portal vein; Child-Pugh class A or B and Eastern Cooperative Oncology Group score of 0-2] and ii) small HCC not amenable to surgery, or small HCC in patients refusing surgery or local radiofrequency/microwave ablation. The contraindications for TACE were i) Child-Pugh class C; ii) severe, uncorrectable coagulation dysfunction; iii) complete obstruction of the main portal vein and few collateral vessels; iv) concomitant infection that could not be treated simultaneously; v) distant metastasis and an estimated survival time of <3 months; vi) cachexia or multiple organ failure; and vii) cancer replacing ≥70% of the liver volume. Informed consent was obtained from each patient prior to treatment and the study protocol was approved by the Beijing 302 Hospital Ethics Committee.

TACE. Following preprocedural preparation, a 5F introducer sheath (Terumo, Tokyo, Japan) was cannulated at the femoral artery by the Seldinger method, and a 5F RH angiographic catheter (Terumo) was advanced to the celiac trunk and superior mesenteric artery, followed by arteriography. The perfusion characteristics of the tumor and portal vein were observed throughout the arterial and late venous phases following injection of contrast media. Following superselective catheterization of the tumor-supplying arteries with a 2.7F micro catheter (Terumo), fluorouracil (0.5-1.0 g), epirubicin (20-40 mg) and a lipiodol emulsion (5-25 ml, depending on the tumor size) were slowly injected to embolize the target vessels. Gelatin sponge particles were used to embolize the tumor-supplying arteries. Following TACE, the catheter and the introducer sheath were removed. The punctured limb was immobilized and the femoral artery puncture site was compressed by an artery compressor (YMIR, Tianjin, China) for 10 h.

Post-TACE management and follow-up. Supportive liver protection therapy (i.e., use of glycyrrhizic acid, glutathione, polyene phosphatidylcholine and ademetionine) was performed routinely after TACE. At 3 and 30 days after TACE, routine blood tests, and measurement of liver function, prothrombin time and prothrombin activity were performed. At 30 days after TACE, enhanced magnetic resonance imaging or enhanced computed tomography scans were performed to determine cancer activity. If complications (infection, upper gastrointestinal bleeding, or decompensated liver function) were present, the hospital stay was prolonged, and appropriate therapies were administered. Decompensated liver function was defined as Child-Pugh class C liver function at 30 days after TACE; leukopenia as a WBC count $<4x10^9$/l; agranulocytosis as a neutrophil count $<0.5x10^9$/l; thrombocytopenia as a platelet count $<100x10^9$/l; and severe thrombocytopenia as a platelet count $<20x10^9$/l. Following TACE, the patients were followed up for 30 days. The primary endpoints were WBC count, PLT count and complications during the perioperative period.

Statistical analysis. Statistical analysis was performed with SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation and qualitative data as rate, and they were compared with the Chi-squared test. Data with a non-normal distribution were compared with the Wilcoxon non-parametric rank sum test. A P-value <0.05 was considered to indicate statistically significant differences.

Results

Baseline characteristics. The medical records of HCC patients (n=1,461) with cirrhosis who received TACE at the Beijing 302 Hospital between January 2012 and December 2013 were retrospectively reviewed. Following exclusion of patients who received a splenectomy (n=104), 1,357 patients who underwent a total of 2,031 TACE procedures were included (Table I). The mean patient age was 54.96 years (range, 24-86 years), there were 1,125 men (82.9%) and 232 women (17.1%), and the mean tumor diameter was 4.55 cm (range, 1-22.8 cm). Child-Pugh class A was present in 1,523 procedures (75%) and class B in 508 procedures (25%). According to the BCLC classification, in 351 procedures (17.3%) the HCC was early-stage, in 1,120 (55.1%) it

Table I. Baseline characteristics of HCC patients with cirrhosis (n=1,357) who underwent TACE procedures (n=2,037).

Characteristics	N (%)
Age (years)	54.96±9.66
Sex	
Male	1,125 (82.9)
Female	232 (17.1)
Tumor number	
1	671 (33)
2	216 (10.6)
≥3	1,144 (56.4)
BCLC stage	
Early	351 (17.3)
Intermediate	1,120 (55.1)
Advanced	560 (27.6)
Vascular involvement	
None	1,637 (80.6)
Branch of portal vein	218 (10.7)
Main portal vein	150 (7.4)
Inferior vena cava	26 (1.3)
Preprocedural PLT count ($x10^9$/l)	
20>PLT≥10	13 (0.6)
30>PLT≥20	54 (2.7)
40>PLT≥30	153 (7.5)
50>PLT≥40	196 (9.7)
60>PLT≥50	171 (8.4)
100>PLT≥60	528 (26)
PLT≥100	916 (45.1)
Tumor diameter (cm)	4.55±3.59
Child-Pugh class	
A	1,523 (75)
B	508 (25)
Number of TACEs	
1	896 (44.1)
2	465 (22.9)
≥3	693 (33)
Metastasis	
No	1,769 (87.1)
Local	111 (5.5)
Distant	151 (7.4)
Preprocedural WBC count ($x10^9$/l)	
2>WBC≥1	141 (6.9)
3>WBC≥2	365 (18)
4>WBC≥3	473 (23.3)
WBC≥4	1,052 (51.8)
Pathology	
Hepatitis B	1,083 (79.8)
Hepatitis C	131 (9.7)
Hepatitis B and C	22 (1.6)
Alcoholic liver disease	50 (3.7)
Others	71 (5.2)

The differences in sex and pathology were based on the number of patients; other differences were compared based on the number of TACE procedures. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; WBC, white blood cell; PLT, platelet; BCLC, Barcelona Clinic Liver Cancer.

was intermediate-stage and in 560 (27.6%) cases it was advanced-stage. The patients were divided into 4 groups based on preprocedural WBC count and into 7 groups based on preprocedural PLT count (Table I). Patients in the lowest PLT count group ($20x10^9$/l>PLT≥$10x10^9$/l) received a PLT infusion prior to TACE.

Incidence of perioperative complications. All the complications that occurred within 30 days after TACE were recorded (Table II). The major complications were decompensated liver function (n=66; 3.25%) and puncture site bleeding (n=45; 2.22%); 15 of these patients had preprocedural PLT counts <$60X10^9$/l, 10 had preprocedural PLT counts 60-$100x10^9$/l and 20 had PLT counts >$100x10^9$/l. Bleeding was attributed to poor local pressurization and, following adjustment of the compressor, it resolved gradually. A total of 33 patients (1.62%) had infections, namely septicemia (n=6), with peritonitis (n=25) and pneumonia (n=2); infection developed in 12 patients with preprocedural WBC counts <$3x10^9$/l, 8 patients with preprocedural WBC counts 3-$4x10^9$/l, and 13 patients with preprocedural WBC counts >$4x10^9$/l. Agranulocytosis occurred in 3 patients (0.15%), including 1 with a preprocedural WBC count <$3x10^9$/l and 2 with preprocedural WBC counts >$4x10^9$/l; following administration of granulocyte colony-stimulating factor (G-CSF), the WBC counts returned to the preprocedural levels. Severe thrombocytopenia occurred in 8 patients (0.39%), including 6 with preprocedural PLT counts <$20x10^9$/l and 2 with preprocedural PLT counts 20-$30x10^9$/l; following administration of interleukin-11 (IL-11), the PLT counts returned to the preprocedural levels at 30 days after TACE. There were 6 cases of upper gastrointestinal bleeding (0.3%) and 4 cases of tumor rupture (0.2%). Other complications, such as ectopic embolism, liver abscess, cholecystitis, skin/mucosal bleeding and acute renal failure, were not observed.

Leukocyte count prior to and following TACE. There were 506 patients with preprocedural WBC counts <$3x10^9$/l, 116 of whom received treatment with G-CSF prior to TACE. Following G-CSF treatment, the WBC count increased in 103 patients, remained unchanged in 3 patients, and decreased in 10 patients (overall efficacy: 88.8%). This suggests that G-CSF was effective for the treatment of leukopenia due to hypersplenism in these patients. G-CSF was also administered to 3 patients who developed agranulocytosis following TACE and their WBC counts increased significantly, suggesting that G-CSF is also effective for chemotherapy-induced agranulocytosis.

WBC counts were analyzed prior to TACE, 3 days after TACE and 30 days after TACE, and patients were divided into tertiles according to the preprocedural WBC count, based on the normal range of 4-$10x10^9$/l and the 2011 Chinese guidelines (12) for the diagnosis and treatment of HCC: $1x10^9$/l≤WBC<$3x10^9$/l; $3x10^9$/l≤WBC<$4x10^9$/l; and $4x10^9$/l≤WBC (Tables III and V). The guidelines for the treatment of HCC in China (12) state that a WBC count <$3x10^9$/l is a contraindication for interventional therapy. Our results demonstrated that the lowest tertile (506 patients) had a WBC count of 2.32±0.476$x10^9$/l prior to TACE, 3.305±1.449$x10^9$/l at 3 days after TACE, and 2.583±0.969$x10^9$/l at 30 days after

Table II. Postoperative major complications of patients (n=1,357) who underwent TACE procedures (n=2,037).

Complications	N (%)
Decompensated liver function	66 (3.25)
Upper gastrointestinal bleeding	6 (0.3)
Tumor bleeding	4 (0.2)
Infection	33 (1.62)
Puncture site bleeding	45 (2.22)
Agranulocytosis	3 (0.15)
Severe thrombocytopenia	8 (0.39)

TACE, transcatheter arterial chemoembolization.

Table III. Infections in HCC patients with different preprocedural WBC counts.

Group ($x10^9$/l)	Infection (n)	No infection (n)	P-value
3>WBC≥1	12	494	0.2498
4>WBC≥3	8	465	
WBC≥4	13	1,039	

Correlation analysis using the Chi-squared test. HCC, hepatocellular carcinoma; WBC, white blood cell.

TACE, and that 73 of these patients (14.4%) had lower WBC counts at 3 days after TACE. The middle tertile (473 patients) had a WBC count of 3.466±0.285x10^9/l prior to TACE, 4.597±1.619x10^9/l at 3 days after TACE, and 3.569±1.040x10^9/l at 30 days after TACE, and 65 of these patients (13.7%) had lower WBC counts at 3 days after TACE. The highest tertile (1,052 patients) had a WBC count of 5.776±1.515x10^9/l prior to TACE, 6.957±2.474x10^9/l at 3 days after TACE, and 5.496±1.605x10^9/l at 30 days after TACE, and 194 of these patients (18.7%) had lower WBC counts at 3 days after TACE. Taken together, these results indicate that the WBC count increased after TACE in the majority of the patients, which was consistent with the findings of Mazioti *et al* (18). For the 3 patients who developed agranulocytosis following TACE, the WBC count increased after treatment with G-CSF and returned to the preprocedural level at 30 days after TACE.

Platelet count prior to and following TACE. A total of 587 patients had preprocedural PLT counts <60x10^9/l, 37 of whom received treatment with IL-11 prior to TACE. The PLT count increased in 12 of these patients, remained unchanged in 12 patients, and declined in 13 patients (overall efficacy: 32.4%). This indicates that IL-11 exhibited a poor efficacy in the treatment of thrombocytopenia due to hypersplenism in HCC patients. A total of 8 patients developed severe thrombocytopenia following TACE, and their PLT counts returned to pre-TACE level with IL-11 treatment, suggesting that IL-11 was effective for the treatment of chemotherapy-induced severe thrombocytopenia. A total of 120 patients had preprocedural PLT counts <60x10^9/l and received PLT transfusion prior to TACE. The PLT count increased in 107 patients, remained unchanged in 5 patients, and decreased in 8 patients (overall efficacy: 89.2%). Thus, PLT transfusion prior to TACE was effective for the treatment of thrombocytopenia due to hypersplenism in HCC patients.

PLT counts were also analyzed prior to TACE, 3 days after TACE, and 30 days after TACE, and patients were divided into tertiles based on the normal range of 100-300x10^9/l and the 2011 Chinese guidelines (12) for the diagnosis and treatment of HCC: 10x10^9/l≤PLT<60x10^9/l; 60x10^9/l≤PLT<100x10^9/l; and PLT≥100x10^9/l (Tables IV and VI). The guidelines for the treatment of HCC in China (12) state that a PLT count <60x10^9/l is a contraindication for interventional therapy. Our results demonstrated that the lowest tertile (587 patients) had a PLT count of 42.721±10.414x10^9/l prior to TACE, 41.210±11.552x10^9/l at 3 days after TACE, and 45.576±13.739x10^9/l at 30 days after TACE; there was an increased PLT count at 3 days after TACE in 206 patients (35.0%) and an increased PLT count in 120 patients who received PLT transfusion or IL-11 treatment (adjusted efficacy: 18.4%). The middle tertile (528 patients) had a PLT count of 78.108±11.765x10^9/l prior to TACE, 70.331±17.338x10^9/l at 3 days after TACE, and 77.068±21.184x10^9/l at 30 days after TACE; there was an increased PLT count at 3 days after TACE in 106 patients (20.1%). The highest tertile (916 patients) had a PLT count of 157.841±50.930x10^9/l prior to TACE, 136.774±50.132x10^9/l at 3 days after TACE, and 148.572±51.417x10^9/l at 30 days after TACE; there was an increased PLT count at 3 days after TACE in 165 patients (18%). A total of 8 patients developed severe thrombocytopenia following TACE, and their PLT counts returned to normal after IL-11 treatment. The PLT count declined at 3 days after TACE in the majority of the patients, consistent with the findings of Mazioti *et al* (18), but returned to the preprocedural level at 30 days after TACE.

Incidence of infection following TACE and association with preprocedural WBC count. A total of 33 patients developed infection after TACE, namely septicemia (n=6), peritonitis (n=25) and pneumonia (n=2) (Table III). Among patients with WBC counts <3x10^9/l, 12/506 developed infections (2.37%); among patients with WBC counts 3-4x10^9/l, 8/473 developed infections (1.69%); and among patients with WBC counts >4x10^9/l, 13/1052 developed infections (1.24%). These 3 groups exhibited no significant differences in the incidence of infection (P>0.05).

Incidence of puncture site bleeding following TACE and association with preprocedural PLT count. Puncture site bleeding occurred in 45 patients (Table IV). Among patients with preprocedural PLT counts <60x10^9/l, 15/587 (2.56%) had bleeding; among patients with preprocedural PLT counts 60-100x10^9/l, 10/528 (1.89%) had bleeding; among patients with preprocedural PLT counts >100x10^9/l, 20/916 (2.18%) had bleeding. These 3 groups exhibited no significant differences in the incidence of puncture site bleeding (P>0.05). Moreover, following adjustment of the compressor, bleeding did not continue. This suggests that improper pressurization is a major cause of puncture site bleeding, rather that the preprocedural PLT count.

Table IV. Puncture site bleeding in HCC patients with different preprocedural PLT counts.

Group ($x10^9$/l)	Bleeding (n)	No bleeding (n)	P-value
60>PLT≥10	15	572	0.7550
100>PLT≥60	10	518	
PLT≥100	20	896	

Correlation analysis using the Chi-squared test. HCC, hepatocellular carcinoma; PLT, platelet.

Table V. WBC counts before and after TACE in HCC patients with different preprocedural WBC counts.

Group ($x10^9$/l)	Before TACE	3 days after TACE	30 days after TACE
3>WBC≥1	2.32±0.476	3.305±1.449[a]	2.583±0.969[a]
4>WBC≥3	3.446±0.285	4.597±1.619[a]	3.569±1.040
WBC≥4	5.776±1.515	6.957±2.474[a]	5.496±1.605[a]

[a]P<0.05 vs. before TACE based on an intragroup comparison with the Wilcoxon non-parametric rank sum test. Data are presented as mean ± standard deviation. HCC, hepatocellular carcinoma; WBC, white blood cell; TACE, transcatheter arterial chemoembolization.

Discussion

The present study is a retrospective analysis of the WBC and PLT counts prior to and following TACE for HCC, and of the perioperative incidence of the complications of TACE in 1,357 patients who received a total of 2,031 TACE procedures. Our results demonstrated that the WBC count increased shortly after TACE, but returned to the pre-TACE level within 30 days, and that the PLT count declined shortly after TACE, but also returned to pre-TACE level within 30 days. There was a very low incidence of agranulocytosis, severe thrombocytopenia, infection and puncture site bleeding following TACE. One of the limitations of the present study is its retrospective, single-center design. In addition, a proportion of patients with reduced WBC counts received G-CSF treatment prior to TACE, and a proportion of patients with reduced PLT counts received IL-11 treatment or PLT transfusion prior to TACE. These treatments may have affected the development of post-operative infection and/or puncture site bleeding.

HCC patients usually have concomitant cirrhosis (10), which is characterized by portal hypertension and decompensated liver function. Reduced WBC and PLT counts are usually secondary to portal hypertension-induced hypersplenism, and closely associated with upper gastrointestinal bleeding, anemia and infection in decompensated cirrhosis patients, which differ from immunodeficiency- or chemotherapy-induced leukopenia or thrombocytopenia. Previous research reported that >76% of cirrhosis patients have concomitant thrombocytopenia (19). For HCC patients with cirrhosis, the reduced PLT count is generally attributed to elevated phagocytosis of PLTs due to hypersplenism (20); in addition, it is also associated with myelosuppression, reduced thrombopoietin and autoimmune dysfunction induced by viral infection or alcohol intake (21,22). TACE is a minimally invasive operation; thus, there is no strict requirement in terms of a preprocedural PLT count. For HCC patients with a low PLT count, TACE is feasible if PLT transfusion is performed prior to the procedure (13,23). A previous study investigated partial splenic embolization in cirrhosis patients with reduced PLT counts, and reported no complications such as puncture site bleeding or skin/mucosal bleeding, whereas the PLT/WBC counts increased significantly following treatment (23). Ooka *et al* (13) performed TACE (n=32) and partial splenic embolization (PSE; n=32) simultaneously in 21 HCC patients with reduced PLT counts (24-49x10^9/l). That study reported that, following TACE, the PLT count increased to >50x10^9/l in 17 of the 21 patients, of whom 13 received systemic chemotherapy, and 2 of the 21 patients developed hematomas (6%). However, it was not mentioned whether the hematomas were caused by the low PLT count, poor coagulation function, or poor pressurization at the puncture site. Ishikawa *et al* (24) performed TACE (n=48) or TACE plus PSE (n=53) in 101 HCC patients with reduced PLT counts. There were no obvious complications after the procedure in either of the two groups, and the PLT count increased significantly after the procedure in the combined therapy group.

Generally, chemotherapy-induced myelosuppression is rare following TACE, but when it does occur it develops within several days after the procedure (25). Buijs *et al* (26) followed 190 HCC patients who received TACE and analyzed the long-term adverse effects. Their results demonstrated that the incidence of grade 3/4 thrombocytopenia was 13% at 6 months and 23% at 12 months, which was significantly lower compared with the rates following systemic chemotherapy. We hypothesized that this type of thrombocytopenia is associated with the deterioration due to cirrhosis after TACE, or is a part of the natural progression of liver disease.

Different countries have different guidelines regarding the PLT count prior to TACE for the treatment of HCC with cirrhosis. International guidelines do not indicate the PLT count as an absolute or relative contraindication for TACE (14-16) (Table VII). The 2011 guidelines in China (12) state that a PLT count <60x10^9/l is a contraindication for TACE. However, leukopenia or thrombocytopenia induced by hypersplenism different from those induced by immunodeficiency or chemotherapy. The use of a PLT count of 60x10^9/l as a cut-off for TACE is unnecessarily restrictive when there are newer options for access site management with closure devices, improved performance of lower profile catheters and newer access techniques, such as radial artery catheterization. Artery compressors have the advantages of short hemostasis time and short immobilization time of the punctured limb (27). A radial arterial access site has the advantages of minimal invasiveness, is easy to compress and achieve hemostasis, with less local bleeding and fewer vascular complications (28). The use of a radial arterial access site and an artery compressor may reduce the incidence of vascular complications following TACE procedures for HCC patients with femoral artery puncture difficulties, poor coagulation function and lower PLT counts. In clinical practice, a proportion of HCC patients with cirrhosis do not

Table VI. PLT counts before and after TACE in HCC patients with different preprocedural PLT counts.

Group ($x10^9$/l)	Before TACE	3 days after TACE	30 days after TACE
60>PLT≥10	42.721±10.414	41.210±11.552[a]	45.576±13.739[a]
100>PLT≥60	78.108±11.765	70.331±17.338[a]	77.068±21.184[a]
PLT≥100	157.841±50.930	136.774±50.132[a]	148.572±51.417[a]

[a]P<0.05 vs. before TACE based on an intragroup comparison with the Wilcoxon nonparametric rank sum test. Data are presented as mean ± standard deviation. HCC, hepatocellular carcinoma; PLT, platelet; TACE, transcatheter arterial chemoembolization.

Table VII. Absolute and relative contraindications to transcatheter arterial chemoembolization (16).

Contraindications
Absolute
Decompensated cirrhosis (Child-Pugh ≥B8)
Extensive tumor with massive replacement of both hepatic lobes
Severely reduced portal vein flow
Technical impediments to hepatic intraarterial treatment
Relative
Kidney failure
Severe cardiopulmonary comorbidities
Tumor size ≥10 cm
Untreated varices at high risk of bleeding
Bile duct occlusion

meet this requirement, even after intravenous PLT transfusion. Thus, use of this threshold may delay or even forestall the administration of TACE. In the present retrospective study of 1357 HCC patients with cirrhosis (2031 procedures), 54.9% were performed with PLT counts <$100x10^9$/l (meeting the diagnostic criteria for thrombocytopenia); 28.9% were performed with PLT counts <$60x10^9$/l; and 13 procedures (0.6%) were performed with PLT counts <$20x10^9$/l (meeting the diagnostic criteria for severe thrombocytopenia). It is difficult to increase the PLT count to $60x10^9$/l by intravenous PLT transfusion in patients with counts <$20x10^9$/l; thus, these patients would not receive TACE if this threshold is applied. Our results demonstrated that in only 8 procedures (0.39%) severe thrombocytopenia developed after TACE, 6 of which met the diagnostic criterion for severe thrombocytopenia prior to TACE. Nonetheless, TACE was successful in these patients after PLT transfusion, none of the patients developed skin/mucosal or cavity bleeding due to a low PLT count, and their PLT counts returned to or even exceeded the preprocedural level following IL-11 treatment.

The reduced PLT count after TACE may be associated with myelosuppression following chemotherapy and PLT consumption due to PLT aggregation. However, the reason for the increased PLT count shortly after TACE was unclear in several of our patients. Previous research reported that acute immune-mediated thrombocytopenia developed in a patient with pancreatic neuroendocrine carcinoma and liver metastasis following TACE. In that patient, the PLT count was $186x10^9$/l prior to TACE and decreased to $7x10^9$/l after TACE, but the WBC count remained unchanged. Biochemical examinations revealed that the PLT-related IgG increased, the patient was non-responsive to PLT transfusion, and the PLT count returned to normal with dexamethasone treatment (29). In the present study, in 45 procedures (2.2%) puncture site bleeding developed after TACE, but the bleeding was controlled following adjustment of the artery compressor in all these cases, suggesting that the bleeding was caused by poor pressurization rather than the reduced PLT count. In 6 procedures, upper gastrointestinal bleeding developed after TACE, which was attributed to esophageal and gastric varices secondary to portal hypertension, rather than to the reduced PLT count. Thus, for HCC patients with cirrhosis, a reduced PLT count due to hypersplenism should not be considered a contraindication for TACE.

A low WBC count in HCC patients with cirrhosis is associated with hypersplenism, reduced production of G-CSF and myelosuppression. Gurakar *et al* (30) reported that the WBC count increased significantly after treatment with G-CSF in patients with cirrhosis and leukopenia. For HCC patients who are scheduled to receive TACE, TACE-induced agranulocytosis and subsequent infection are the major concerns if a low WBC count is present prior to the procedure. Currently, the consideration of the WBC count for performing TACE differs among the guidelines of different countries. The international guidelines for TACE in HCC patients do not consider an abnormal WBC count as an absolute or relative contraindication (14-16) (Table VII). However, the 2011 Chinese guidelines for the treatment of HCC (12) indicate a WBC count <$3x10^9$/l as a contraindication to TACE, although not an absolute contraindication; these guidelines also mention that a low WBC count due to hypersplenism is different from a chemotherapy-induced reduction in the WBC count. A previous study reported that a low WBC count was an independent predictor of liver abscess following TACE (31); however, 25 patients with liver cancer (12 with HCC and 13 with secondary liver cancer) in that study received choledochojejunostomy prior to TACE, and the incidence of liver abscess was as high as 26.2% (17/62 procedures). Another study reported that the incidence of liver abscess in patients with liver cancer was only 2% after TACE (32). That study also examined risk factors such as diabetes, neutropenia and choledochojejunostomy, and the results only indicated choledochojejunostomy as an independent risk factor for liver abscess. In the 7 patients with liver abscesses, the preprocedural WBC count was 5.5±$1.7x10^9$/l (range, 3.3-$8.2x10^9$/l).

The present retrospective analysis of 1,357 HCC patients with cirrhosis (2,031 procedures) demonstrated that in 48.2% of the procedures the WBC counts were $<4x10^9$/l prior to TACE (meeting the diagnostic criterion for leukopenia); in 24.9% of the procedures the WBC counts were $<3x10^9$/l; and in 6.9% of the procedures the WBC counts were $<2x10^9$/l. Our analysis also indicated that in only 16.3% of the procedures the WBC counts were reduced at 3 days after TACE. The increase in the WBC count following TACE is associated with the postoperative embolism syndrome (24), and a reduction in the WBC count is associated with chemotherapy-induced myelosuppression. In only 3 procedures (0.15%) agranulocytosis developed after TACE, but the WBC counts returned to pre-TACE levels following G-CSF treatment. None of the patients developed leukopenia-related skin/mucosal infection.

In 33 of the procedures infections developed after TACE; 2 of these patients with lung infections had chronic bronchitis and diabetes, and their preprocedural WBC counts were $>4x10^9$/l. The presence of peritonitis (n=25) and septicemia (n=6) were mainly associated with postoperatively decompensated liver function and intestinal bacterial translocation. Our results demonstrated that the postoperative incidence of infection was 2.37% (12/506) in the lowest WBC count tertile, 1.69% (8/473) in the middle WBC count tertile, and 1.24% (13/1052) in the highest WBC count tertile, with no significant difference among these groups (P>0.05). Kirchhoff *et al* (33) investigated 47 patients with advanced liver cancer who received chemoembolization with degradable starch microspheres and lipiodol (a total of 112 TACE procedures), and only 7.1% (n=8) and 3.6% (n=4) developed reversible grade 3-4 leukopenia and thrombocytopenia, respectively. Thus, for HCC patients with cirrhosis, a reduced WBC count due to hypersplenism should not be considered as an absolute contraindication for TACE.

In conclusion, TACE is safe for HCC patients with preprocedural thrombocytopenia or leukopenia due to hypersplenism, and the postoperative incidence of major complications, such as decompensated liver function, tumor bleeding, upper gastrointestinal bleeding, severe thrombocytopenia, agranulocytosis, infection and puncture site bleeding, is very low. Thrombocytopenia or leukopenia due to hypersplenism should not be considered as an absolute contraindication to TACE among these patients. These conditions simply place the patients at a potentially increased risk and must be weighed against the overall clinical status and other existing risk factors.

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