Hepatotoxicity after Transarterial Chemoembolization and Transjugular Intrahepatic Portosystemic Shunt: Do Two Rights Make a Wrong?

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ABSTRACT

Purpose: To compare the rates of hepatotoxicity after transarterial chemoembolization for hepatocellular carcinoma (HCC) in patients with and without a transjugular intrahepatic portosystemic shunt (TIPS) who were stratified into comparable risk groups.

Materials and Methods: A retrospective review of patients with HCC who were treated with transarterial chemoembolization between January 2005 and December 2009 was performed. Of 158 patients with comparable model for end-stage liver disease (MELD) scores, 10 had a patent TIPS. Hepatobiliary severe adverse events (SAEs) occurring after transarterial chemoembolization were documented. In addition, 1-year survival and liver transplantation rate after transarterial chemoembolization were calculated in each group.

Results: The incidence of hepatobiliary SAEs after transarterial chemoembolization was nearly two times higher in patients with a TIPS (70%) than in patients without a TIPS (36%; $P = .046$). The liver transplantation rate 1 year after transarterial chemoembolization was 2.5 times higher in patients with a TIPS (80%) than in patients without a TIPS (32%; $P = .004$). There was no significant difference in 1-year survival between the two groups after transarterial chemoembolization.

Conclusions: Patients with HCC and a patent TIPS are more likely to develop significant hepatotoxicity after transarterial chemoembolization than comparable patients without a TIPS in place.

ABBREVIATIONS

CPT = Child-Pugh-Turcotte; HCC = hepatocellular carcinoma; MELD = model for end-stage liver disease; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = severe adverse event; TIPS = transjugular intrahepatic portosystemic shunt

Hepatocellular carcinoma (HCC) is the second most frequent cause of cancer death worldwide in men and the sixth leading cause of cancer death in women (1,2). Transplantation and surgical resection are considered to be the only curative treatments (3–5). Only a small percentage of patients with HCC are candidates for resection (6,7). Liver-directed therapies are widely used to "bridge" patients to transplant or to treat patients with unresectable HCC (8). Transarterial chemoembolization has become a commonly employed treatment for HCC (9–11). However, hepatic dysfunction is frequently observed after chemoembolization (12,13).

In addition to predisposing patients to HCC, cirrhosis leads to portal hypertension (14). A transjugular intrahepatic portosystemic shunt (TIPS) is an important therapeutic option in managing the complications of portal hypertension, such as variceal bleeding and refractory ascites (15). Some patients who have undergone a TIPS procedure for the treatment of complications related to portal hypertension are later found to have HCC and require therapy for the cancer. However, such patients are not considered ideal candidates for transarterial chemoembolization because of the diversion of the portal venous flow via the TIPS. Previous reports of transarterial chemoembolization in patients with a TIPS have included case reports or small patient series without direct comparison with a

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control, non-TIPS group (16–20). The purpose of our study was to compare the rates of hepatotoxicity after transarterial chemoembolization for HCC in patients with and without a patent TIPS who were stratified into comparable risk groups.

MATERIALS AND METHODS

Patients

Our study was approved by our institutional review board. An informed consent requirement was waived. A retrospective record review of patients who underwent transarterial chemoembolization at our institution between January 2005 and December 2009 was performed. We identified 10 patients who had a patent TIPS at the time of the transarterial chemoembolization procedure within the specified 5-year time period. Calculated model for end-stage liver disease (MELD) scores for the patients ranged from 10–18. A TIPS procedure had been performed on six patients for secondary prevention of variceal bleeding. The remaining four patients had undergone a TIPS procedure because of refractory ascites.

Seven patients had undergone the TIPS procedure at another institution, and records from the procedure were unavailable for review. The remaining three patients underwent the TIPS procedure at our institution using previously described techniques (21). A GORE VIATORR stent graft (W.L. Gore & Associates, Flagstaff, Arizona) was used for shunt creation in two cases, with the TIPS in the third case formed using a WALLSTENT (Boston Scientific, Natick, Massachusetts). In all three cases, a decrease in portosystemic gradient was noted from 32 mm Hg to 11 mm Hg, 20 mm Hg to 10 mm Hg, and 32 mm Hg to 8 mm Hg. We identified 148 patients with comparable MELD scores who did not have a TIPS and were treated with transarterial chemoembolization in the same 5-year time period to serve as the control population. All patients were also classified using the Child-Pugh-Turcotte (CPT) classification system. All patients had a diagnosis of HCC, which was based on European Association for the Study of the Liver guidelines (22). Characteristics of the patient population are summarized in **Table 1**.

TIPS patency was confirmed using Doppler abdominal ultrasound performed within 6 months of the transarterial chemoembolization procedure as part of routine clinical care. In all patients with a TIPS, vascular flow was present throughout the entire shunt, and midshunt velocities were $>$ 60 cm/s. Based on prior reports (25,26), midshunt velocities $>$ 60 cm/s were considered a reliable indicator of TIPS patency.

Transarterial Chemoembolization Regimen

Transarterial chemoembolization was performed with a combination of doxorubicin hydrochloride (25 mg), mitomycin C (10 mg), and cisplatin (50 mg) administered in a 1:1 emulsion with ethiodized oil (Ethiodol; Laboratoires Guerbet, Roissy, France). The aqueous component for the emulsion was Omnipaque 350 contrast agent (Amersham Pharmacia Biotech, Piscataway, New Jersey). The transarterial chemoembolization regimen was similar for patients with and

Table 1. Patient Characteristics

Variables	TIPS Group (n = 10)	Non-TIPS Group (n = 148)	*P* Value
Age (y), median (range)	59 (51–72)	59 (40–82)	.79
Male gender, number of patients (%)	9 (90)	124 (84)	.99
MELD score, median (range)	15 (10–18)	12 (10–18)	.35
CPT score, median (range)	7 (5–11)	7 (5–12)	.61
Child-Pugh class, number of patients (%)			.12
A	5 (50)	41 (28)	
B	3 (30)	89 (60)	
C	2 (20)	18 (12)	
Cause of cirrhosis, number of patients (%)			.19
Viral hepatitis	6 (60)	115 (78)	
Alcohol	1 (10)	9 (6)	
NASH	2 (20)	8 (5)	
Other/combination	1 (10)	16 (11)	
BCLC stage, number of patients (%)			.97
0	1 (10)	17 (11)	
A	5 (50)	77 (52)	
B	2 (20)	26 (18)	
C	0 (0)	7 (5)	
D	2 (20)	21 (14)	

BCLC = Barcelona Clinic Liver Cancer (23,24, CPT = Child-Pugh-Turcotte, MELD = model for end stage liver disease, NASH = nonalcoholic steatohepatitis, TIPS = transjugular intrahepatic portosystemic shunt.