

Prevention of Variceal Rebleeding in Cirrhotic Patients with Advanced Hepatocellular Carcinoma Receiving Molecularly-targeted Therapy: a randomized pilot study Transjugular Intrahepatic Portosystemic Shunt Versus Endoscopic plus β -blocker

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Abstract

Background Although transjugular intrahepatic portosystemic shunt (TIPS) is recommended for secondary prophylaxis of variceal bleeding if standard therapy fails and for patients with high-risk of recurrent bleeding, no guidelines for the treatment of symptomatic portal hypertension in HCC patients are available. This study aimed to compare the efficacy and safety of TIPS with endoscopic+ β -blocker for prevention of the rebleeding in such patients.

Methods 106 consecutive advanced HCC patients receiving tyrosine kinase inhibitor (TKI) who had been treated with vasoactive drugs plus endoscopic therapy for variceal bleeding were randomly assigned to receive either TIPS (n=52) or endoscopic+ β -blocker therapy (n=54) for the prevention of rebleeding. The primary endpoint was variceal rebleeding after randomization.

Results

During a median follow-up of 16 months, rebleeding occurred in 14 patients in the endoscopic+ β -blocker group and 3 patients in the TIPS group ($P<0.001$). Forty-nine patients died (38 in endoscopic+ β -blocker group and 11 in TIPS group, $P<0.001$). The 6-, 12-, and 18-month overall survival rates were 95, 81, and 73% for TIPS group and 35, 21, and 15% for endoscopic+ β -blocker group, respectively ($P<0.001$). Eight patients in endoscopic+ β -blocker group received TIPS as rescue therapy, but two died. TKIs was discontinued in 32 patients, including 24 in the endoscopic+ β -blocker group and 8 in the TIPS group ($P<0.001$). No significant differences were observed between the two groups with respect to serious adverse events.

Conclusions In advanced HCC patients receiving TKIs and presented with variceal bleeding, the use of TIPS was associated with significant reduction in rebleeding, improved a higher adherence to TKIs therapy, and prolonged survival.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer death worldwide[1]. The majority of patients with HCC are diagnosed late in its course, rendering them carries a grim prognosis due to lack of systemic therapies[2]. Recently, the treatment landscape for advanced HCC has expanded rapidly, with the approvals of several oral tyrosine kinase inhibitors (TKIs, *e.g.*, sorafenib, lenvatinib, donafenib, regorafenib, and cabozantinib), as well as immune check point inhibitors (*e.g.*, atezolizumab, nivolumab and pembrolizumab) and tumor angiogenesis inhibitors (*e.g.*, bevacizumab, ramucirumab)[3]. Ideal use of these agents in clinics has improved the long-term outcome of patients with advanced HCC as well as introduced hemorrhagic events, such as epistaxis, gastrointestinal hemorrhage/bleeding and pulmonary hemorrhage[4, 5]. Variceal bleeding from any source is increased in advanced HCC patients who are receiving TKIs, which resulted in some advanced HCC patients losing the opportunity for further tumor treatment with TKIs. Therefore, it is a critically important issue to manage variceal bleeding, especially the prevention of rebleeding in advanced HCC patients who are receiving TKIs and presented with portal hypertension.

The current treatment approaches for variceal bleeding include vasoactive drugs, endoscopic therapy, and transjugular intrahepatic portosystemic shunt (TIPS)[6]. Endoscopy can be used to identify the source of bleeding, as well as a hemostatic treatment for actively bleeding lesions[6, 7]. However, endoscopic therapy is

limited in value for variceal bleeding due to a lack of reducing the portal pressure. TIPS effectively reduces intravascular pressure in the portal venous system, and it is thus an ideal therapy in the management of portal hypertensive and prevention of rebleeding[8]. Although preemptive TIPS has become the standard of care in patients with high-risk acute variceal bleeding[9], TIPS is contraindicated in HCC patients with portal hypertension due to the risk of postoperative liver failure, severe complications, and low survival rate for HCC patients[6, 8–11]. Based on our previous clinical experience[12–14], TIPS combined with anti-tumor therapy is safe and effective for the prevention of rebleeding in HCC patients with portal hypertension. However, these data were from single-center studies. Whether TIPS or endoscopic + β -blocker therapy is more beneficial for the prevention of rebleeding in advanced HCC patients who are receiving TKIs, especially regarding incidence of continuation of TKIs and achievement of a survival benefit, is still unknown. The aim of this study was to compare the efficacy and safety of TIPS with endoscopic + β -blocker for the prevention of variceal rebleeding in such patients.

Materials And Methods

Study Design and Participants

This is a multicenter randomized, controlled trial was conducted between October 2018 and December 2020 in three tertiary hospitals, China. Patients would be eligible for the study if they were advanced HCC patients who are receiving TKI and presented with variceal bleeding. The study protocol was approved by the ethics committees of all participating hospitals and followed the Guidelines for Good Clinical Practice in clinical trials. This study was conducted in accordance with the 1975 Declaration of Helsinki, and written informed consent was obtained from all patients after being fully informed of each procedure. The inclusion criteria were: 1) Barcelona Clinic Liver Cancer stage C patients who are receiving TKI presented with a first episode of endoscopically documented variceal bleeding; 2) hemostasis and stabilization were successfully achieved with vasoactive drugs or endoscopy; 3) liver cirrhosis (diagnosed based on clinical presentation, laboratory tests, images) with Child–Pugh–Turcotte score ≤ 13 . Exclusion criteria were: 1) uncontrolled bleeding before randomization; 2) Child–Pugh–Turcotte scores > 13 ; 3) bleeding from isolated gastric or ectopic varices; 4) a history of serious or refractory hepatic encephalopathy (HE); 5) a history of significant heart failure (New York Heart Association class III and IV); 6) pulmonary hypertension previous; 7) TIPS; 8) sepsis and/or multiorgan failure.

Management of Patients

After stabilization and successful vasoactive drugs or endoscopic hemostasis, eligible patients were randomly assigned in a 1:1 ratio to receive TIPS placement or endoscopic + β -blocker. The randomization sequence was generated by a computer with the use of a concealed block size of four. The sample size was based on the assumption that the rate of development of variceal rebleeding would be 29% in long-term endoscopic + β -blocker group at the end of 1 year[15], and 7.8% after TIPS placement[16]. The sample size was determined to be 106 patients, with a dropout rate of 15%, an alpha level of 0.05 and a power of 80%.

Treatment

Hemodynamic stabilization and sustained endoscopic hemostasis were in the Supplementary Materials.

In the endoscopic + β -blocker group, endoscopic variceal ligation (EVL) for esophageal varices and N-butyl cyanoacrylate (HistoAcryl; B. Braun, Melsungen, Germany) injection for gastric varices in combination with β -blocker (preferably slow-release propranolol, titrated to the maximum tolerated dose at rest by 25%, with a lowest limit of 50 beats per minute) was started at day 5 after the index bleeding, unless a contraindication was present (severe arrhythmia, severe obstructive chronic obstructive pulmonary disease, or known intolerance). Elective EVL sessions, which were started 2 weeks after the index bleeding, were performed every 2–4 weeks thereafter until eradication of varices, followed by endoscopic surveillance and retreatment, if indicated, every 6 months.

In the TIPS group, the TIPS placement was performed under sedation anesthesia with propofol and remifentanyl. The right jugular vein was punctured, and a 10-Fr Ring Transjugular Intrahepatic Access Set (Arrow, Reading, PA, United States) was advanced into the vessel. The needle (16-gauge Colapinto, Optimed, Germany) direction, which was used to puncture into the portal system, was estimated according to the location of the tumor thrombus. TIPS with covered stents (Fluency; Bard, Tempe, AZ, United States), were used with initial balloon dilatation to 8 mm, aiming to decrease the portosystemic pressure gradient (PPG) to less than 12 mmHg (or decline of 50%). After simultaneous needle withdrawal and contrast agent injection, the appearance of a “grid-like outline” in the tumor thrombus interspaces, or occasionally, small branches, was considered to indicate successful puncture of the portal system (Supplementary Fig. 1). TIPS function was primarily monitored by clinical evaluation every 6 weeks to 3 months. When signs of possible dysfunction were present (new onset or progressive ascites, or variceal rebleeding), duplex ultrasound was performed.

Outcomes and Follow-up

The primary endpoint was rebleeding. After secondary prevention treatment, new melena or hematemesis occurs again after the stool color is normal, resulting in hospitalization, blood transfusion or hemoglobin decrease of at least 3 g/L, which was defined as rebleeding. Variceal rebleeding was further divided into failure to control bleeding (within 120 hours after index endoscopic treatment) or failure of secondary prophylaxis (after 120 hours) according to the Baveno VI criteria[17]. The secondary endpoints were occurrence of treatment failure (either switch to other therapy or death), discontinuation of TKIs therapy, HE, overall survival (OS), and progression-free survival (PFS) based on clinical parameters. The TKIs dose reduction and drug discontinuation criteria are previously reported[18].

Safety Evaluation

Major postoperative complications defined as grade 3 and above according to the Clavien-Dindo classification[19]. Morbidity and mortality were defined as complications and death occurring within 90 days after the procedure. TKI-related adverse events (AEs) were evaluated using CTCAE version 4.0. OS was calculated as the time from initial intervention to death or the last follow-up.

Statistical Analysis

Patients were censored at the time of loss-to-follow-up or last outpatient visit before study closure. In addition to the censoring time points in the intention-to-treat analysis, patients were censored at the moment they switched therapy. Student's t tests and χ^2 tests were performed to compare continuous and categorical variables, respectively. Data are expressed as median (interquartile range) and number (percentage) when appropriate. Kaplan-Meier (event-free) survival analyses with log-rank tests and Cox's proportional hazard analyses were performed for the endpoints, including rebleeding, treatment failure, death, and HE. In case of zero events in one

group, likelihood ratio test with Firth's correction and 95% hazard ratio profile with likelihood confidence limits were used. All variables with $P < 0.05$ evaluated by univariate analysis were subjected to multivariate analysis. All analyses were performed using the IBM SPSS statistics software v. 25 (IBM Corporation, Armonk, NY, USA). A two-sided P value < 0.05 was considered statistically significant.

The study is registered with ClinicalTrials.gov, Identifier: NCT02477384.

Results

Patients, Recruitment, and Follow-up

The flow diagram of patients enrolled in this study is displayed in Supplementary Fig. 2. A total of 106 patients were included and randomly assigned to either the TIPS group (52 patients) or the endoscopic + β -blocker group (54 patients) after a median of 5 days from index bleeding (interquartile range [IQR]: 3–8). Among them, the most common distribution of etiology was HBV-related HCC (78%). Portal vein tumor thrombus (PVTT) classification[20], the proportion of Vp2, Vp3, Vp4 were 52, 29 and 19%, respectively, in the TIPS group and 54, 33 and 13%, respectively, in the endoscopic + β -blocker group ($P = 0.658$, Table 1). The baseline variables were comparable between the two groups. Two (4%) of the fifty-four patients who were randomized to the endoscopic + β -blocker group crossed over to the TIPS group due to refractory ascites. The median follow-up time was 16.1 months (range, 4.2–24.6 months) for the endoscopic + β -blocker group and 16.2 months (range, 13.0–28.8 months) for the TIPS group ($P = 0.186$, Table 2). Three patients (3%; 2 in the endoscopic + β -blocker group, 1 in the TIPS group) were lost-to-follow-up after a median of 14.2 months (range, 5.2–20.3 months).

Table 1
Patient Demographics and Clinical Parameters

Variables	Endoscopic + β -blocker group	TIPS group	P value
	(n = 54)	(n = 52)	
Age (years), (Mean \pm SD)	53.72 \pm 1.27	57.31 \pm 1.25	0.456
Male (n, %)	46 (86.79)	42 (79.25)	0.842
Etiology (n, %)			0.896
HBV	43(79.62)	40(76.92)	
HCV	3(5.56)	3(5.77)	
Alcohol	3(5.56)	2(3.85)	
Other	5(9.26)	7(13.46)	
Child-Pugh-Turcotte class (n, %)			0.579
A	5 (9.26)	2 (3.85)	
B	37 (68.52)	36 (69.23)	
C	12 (22.22)	14 (26.92)	
Child-Pugh-Turcotte score (Mean \pm SD)	7.87 \pm 2.63	8.16 \pm 2.12	0.412
β -blocker prophylaxis before index bleed (n, %)	8 (15.09)	5 (9.43)	0.337
Ascites (n, %)	37 (68.51)	39(75.00)	0.459
Previous episode of hepatic encephalopathy (n, %)	3(5.56)	0 (0)	0.255
Hemoglobin at enrollment (g/L), (Mean \pm SD)	62.7 \pm 10.7	64.2 \pm 9.1	0.153
INR, median, (range) (P25, P75)	1.20(1.13–1.31)	1.31(1.16–1.48)	0.349
Median Alanine Transaminase (U/L)	54 (32- 89.5)	54 (33-107.5)	0.162
Median Bilirubin (μ mol/L) (P25, P75)	23.55(16.48–50.33)	29.55(20.48–40.98)	0.482
Albumin (g/L), (Mean \pm SD)	30.44 \pm 0.58	31.67 \pm 1.15	0.645
Median Platelet Count (10^9 /L) (P25, P75)	95.50(66.00-146.00)	93.00(56.00-173.70)	0.255
Location of varices at index gastroscopy			0.240
Esophageal varices only	42 (77.78)	45 (86.54)	
Esophageal and gastric varices	12 (22.22)	7 (13.46)	
Barcelona Clinic Liver Cancer Stage			1.000
C	54(100)	52(100)	

Variables	Endoscopic + β -blocker group	TIPS group	<i>P</i> value
	(n = 54)	(n = 52)	
Portal vein tumor thrombus			0.658
Vp2	29(53.70)	27(51.92)	
Vp3	18(33.33)	15(28.85)	
Vp4	7 (12.97)	10(19.23)	
Endoscopic treatment at time of index bleeding			0.583
Band ligation (n, %)	37	33	
Injection sclerotherapy (n, %)	17	19	
Vasoactive-drug therapy at time of index bleeding			0.963
Octreotide (n, %)	26	27	
Somatostatin (n, %)	21	19	
Terlipressin (n, %)	7	6	
Targeted therapy drugs			0.327
Sorafenib (n, %)	20 (37.04)	15 (28.84)	
Lenvatinib (n, %)	34 (62.96)	37 (71.16)	
Prior treatment (n, %)	28(51.85)	27(50.00)	0.994
Resection	4	3	
RFA	7	12	
TACE	13	12	
HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; RFA, radiofrequency ablation.			

Table 2
Summary of outcome measurements

Variables	Endoscopic + β -Blocker Group	TIPS Group	P value
	(n = 54)	(n = 54)	
Median follow-up time(month), (P25, P75)	16.1 (4.2–24.6)	16.2 (13.0-28.8)	0.186
Overall survival rate, %			< 0.001
6 months	35	95	
12 months	21	81	
18 months	15	73	
Progression free survival, %			< 0.001
6 months	23	91	
12 months	19	51	
18 months	15	33	
Rebleeding, n (%)	14 (25.92)	3 (5.56)	< 0.001
Chang of Child-Pugh scores			< 0.001
Improving	8 (14.81)	41(75.92)	
Stable	12(22.22)	5(9.26)	
Worsening	34(62.96)	8(14.82)	
Rebleeding time (month), (Mean \pm SD)	4.1 \pm 1.01	7.2 \pm 1.47	0.556
Treatment failure, n (%)	12 (22.22)	1(1.85)	< 0.001
Death individual, n (%)	38 (70.37)	11(20.37)	< 0.001
Causes of death, n (%)			0.032
Variceal rebleeding	14/38(36.84)	0(0)	
Sepsis/pneumonia	3/38(7.89)	1/11(9.09)	
Liver failure	7/38(18.42)	4/11(36.36)	
HCC progression	14/38(36.84)	6/11(54.55)	
Maintenance TKI full dose, n (%)	3 (7.41)	28 (51.85)	< 0.001
TKIs dose reduction, n (%)	26 (48.15)	18 (33.33)	0.118
Sorafenib	7	9	
Lenvatinib	19	9	
TKI discontinuation, n (%)	25 (46.29)	8 (14.82)	< 0.001
Sorafenib	12	4	

Variables	Endoscopic + β -Blocker Group	TIPS Group	P value
	(n = 54)	(n = 54)	
Lenvatinib	13	4	
IQR, interquartile range; TKI, tyrosine kinase inhibitor.			

Treatments

In the endoscopic + β -blocker group, a total of 129 upper endoscopies (mean, 2.8 ± 2.4 per patient) were performed in the first year after randomization. The majority (71%) of procedures included EVL with placement of a mean 4.6 bands per procedure, 8% included injection N-butyl cyanoacrylate therapy, and in 21% no treatment was considered necessary. Propranolol slow release, titrated on heart rate and/or tolerance, was used for all but 3 patients.

In the TIPS group, 52 patients received one stent and 2 patients two stents. Median time from bleeding to TIPS was 7 days (IQR, 4–12). Twenty-three patients received TIPS within the first 6 days of the index bleeding, and 31 underwent TIPS after 7 days or later (median, 9). Collateral embolization was performed in 4 patients. The 1-year patency rate was 94.6%; 3 patients underwent a successful revision of the TIPS for partial/complete occlusion.

Primary Endpoints: Rebleeding

During follow-up, 14 (27%) patients in the endoscopic + β -blocker group experienced a total of 20 variceal rebleeds compared to 3 (5.6%) patients in the TIPS group who experienced a total of 3 variceal rebleeds ($P < 0.001$; Fig. 1A and Table 2). Among the 14 patients with rebleeding in the endoscopic + β -blocker group, 6 patients experienced the first rebleed during follow-up, 8 patients experienced the second rebleed and received TIPS as a rescue therapy, of whom two died. Among the 3 patients with rebleeding in the TIPS group, all switched to receive a TIPS revision with embolization of varices. Univariate analysis revealed that 2 factors were significantly related to rebleeding after initial intervention. In the multivariate analyses, only the endoscopic + β -blocker (HR 7.548; 95% CI: 2.513–22.668; $P < 0.001$) was an independent poor predictor of rebleeding after initial intervention (Table 3).

Table 3
Univariate and Multivariate Analysis of Rebleeding

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment, endoscope/TIPS	1.90 (1.24, 2.90)	< 0.001	7.55 (2.51–22.67)	< 0.001
Lenvatinib, yes/no	1.20 (0.79, 1.82)	0.139		
Age > 60, yes/no	1.26 (0.83, 1.91)	0.279		
Child-Pugh-Turcotte C, yes/no	1.47 (0.96, 2.26)	0.078		
Albumin > 35, yes/no	0.52 (0.34, 0.80)	0.033	0.56 (0.18–1.79)	0.329
Total bilirubin > 17.1, yes/no	1.68 (1.01, 2.80)	0.267		
Platelet > 100·10 ⁹ /L, yes/no	0.99 (0.66, 1.46)	0.728		
Ascites, yes/no	1.14 (0.74, 1.75)	0.704		
Vp3 and/or Vp4, yes/no	1.09 (0.72, 1.66)	0.302		
HR, hazard risk; TIPS, transjugular intrahepatic portosystemic shunt; Vp3: presence of the thrombus in the first-order branches; Vp4: tumor thrombus in the main trunk of the portal vein and/or a portal vein branch contralateral to the primarily involved lobe.				

Secondary Endpoints: Mortality and Discontinuation of TKI

Thirty-eight (73%) patients in the endoscopic + β -blocker group died, compared to 11

(20%) patients in the TIPS group ($P < 0.001$; Table 2). The causes of death in the endoscopic + β -blocker group included HCC progression in 14/38 (37%), rebleeding in 14/38 (37%), liver failure in 7/38 (18%), sepsis/pneumonia in 3/38 (8%), and in the TIPS group they included HCC progression in 6/11 (55%), liver failure in 4/11 (36%), sepsis/pneumonia in 1/11 (9%) (Table 2). There was a significant difference in the mortality from rebleeding between the two groups ($P = 0.032$; Table 2). The 6-, 12- and 18-month OS rates after initial intervention were 23, 19 and 15%, respectively, in the endoscopic + β -blocker group and 91, 51 and 33%, respectively, in the TIPS group ($P < 0.001$, Table 2 and Fig. 1C). Univariate analysis identified 6 factors that were significantly related to OS. In the multivariate analyses, the endoscopic + β -blocker (HR 11.05 95% CI: 4.73–25.82; $P < 0.001$), discontinuation of TKIs (HR 9.07; 95% CI: 3.54–23.12; $P < 0.001$), Child-Pugh-Turcotte C (HR 3.42; 95% CI: 1.36–8.63; $P = 0.009$) and rebleeding (HR 2.97; 95% CI: 1.50–6.89; $P = 0.036$) were identified as independent poor predictors of OS (Table 4).

Table 4
Univariate and Multivariate Analysis of overall survival and progression free survival

	Overall survival				Progression free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Treatment, endoscopy / TIPS	8.91 (4.46, 17.80)	< 0.001	11.05 (4.73–25.82)	< 0.001	3.31 (2.03, 5.40)	< 0.001	3.31 (1.89–5.80)	< 0.001
TKI discontinuation, yes/no	8.17 (4.16, 14.37)	< 0.001	9.07 (3.54–23.12)	< 0.001	1.27 (0.69, 3.36)	0.023	1.05 (0.54–2.12)	0.857
Age > 60, yes/no	1.63 (0.87, 3.08)	0.131			1.38 (0.83, 2.28)	0.214		
Child-Pugh-Turcotte C, yes/no	0.44 (0.21, 0.91)	0.026	3.42 (1.36–8.63)	0.009	1.88 (1.08, 3.30)	0.027	1.98 (1.06–3.70)	0.032
Albumin > 35, yes/no	2.38 (1.24, 4.57)	0.007	1.55 (0.64–3.73)	0.333	2.05 (1.23, 3.41)	0.005	0.82 (0.44–1.53)	0.537
Total bilirubin > 17.1, yes/no	1.14 (0.55, 2.36)	0.717			1.21 (0.62, 2.36)	0.578		
Platelet > 100·10 ⁹ /L, yes/no	0.65 (0.37, 1.15)	0.135			0.78 (0.49, 1.25)	0.293		
Ascites, yes/no	1.73 (0.86, 3.46)	0.119			1.68 (0.96, 2.94)	0.066		
Vp3 and/or Vp4, yes/no	2.26 (0.98, 3.93)	0.023	1.27(0.499–3.896)	0.634	1.65 (1.00, 2.72)	0.048	1.64 (0.84–3.19)	0.149
Variceal rebleeding, yes/no	2.43 (1.33, 4.42)	0.004	2.97(1.499–6.896)	0.036	1.72 (0.98, 3.03)	0.056		
HR, hazard risk; TIPS, transjugular intrahepatic portosystemic shunt; TKI, tyrosine kinase inhibitor; Vp3: presence of the thrombus in the first-order branches; Vp4: tumor thrombus in the main trunk of the portal vein and/or a portal vein branch contralateral to the primarily involved lobe.								

Fifty (96%) patients with TKIs treatment in the endoscopic + β -blocker group were down-dosed, compared to 26 (48%) patients in the TIPS group ($P < 0.001$; Table 2). Among them, 25 patients (48%) in the endoscopic + β -blocker group and 8 patients (15%, $P < 0.001$, Table 2) in the TIPS group were permanently discontinuation. The causes of permanently discontinuation of TKIs in the endoscopic + β -blocker group included rebleeding in 14

(58%), HCC progression in 6 (25%), TKIs-related AEs in 3 (12%), and severe liver function deterioration in 2 (8%), and in the TIPS group HCC progression in 3 (37%), TKIs-related AEs in 3 (37%), hepatic Encephalopathy in one (13%), and rebleeding in one (13%). Compared to the endoscopic + β -blocker group, the TIPS group had a greater proportion of patients receiving full dose of TKI (52% vs. 4%, $P < 0.001$, Table 2), and a lower proportion of patients with discontinuation of TKIs (15% vs. 48%, $P < 0.001$, Table 2). After all the patients who interrupted TKIs therapy due to variceal bleeding had undergone the endoscopic + β -blocker or TIPS, and were back to TKI therapy again, 8 (8/28, 29%) receiving sorafenib and 9 (9/65, 14%) receiving lenvatinib experienced at least one variceal rebleeding ($P = 0.085$, Fig. 1B).

Secondary Endpoints: Treatment Failure, Hepatic Encephalopathy, and PFS

Twelve (23%) patients in the endoscopic + β -blocker group had a treatment failure, 6 patients switched to TIPS as rescue therapy and 8 patients died during hospitalization, compared to one patient in the TIPS group, of whom died during hospitalization ($P < 0.001$; Table 2). HE occurred in 16 patients (16/106, 15%) in total, including 11(11/54, 20%) in the TIPS group (one case of grade III , 4 grade II , and 6 grade I) and 5(5/52, 9%) in the endoscopic + β -blocker group (2 grade III and 3 grade II , $P = 0.122$; Table 5). Treatments consisted of lactulose ($n = 12$) and/ or rifaximin ($n = 3$) and shunt closure in one TIPS-treated patient with refractory encephalopathy.

Table 5
Adverse events of secondary prophylaxis after variceal bleeding

Variables	Endoscopic + β -Blocker Group	TIPS Group	P value
	(n = 54)	(n = 54)	
No. of Patients (%)	31 (57.41)	24 (44.44)	0.178
Complication of portal hypertension			
Hepatic encephalopathy	5/54(9.26)	11/54(20.37)	0.104
Ascites	15/54(27.78)	2/54(3.70)	< 0.001
Spontaneous bacterial peritonitis	2/54(3.70)	1/54(1.85)	1.000
Hepatorenal syndrome	7/54(12.97)	2/54(3.70)	0.161
Acute-on-chronic liver failure	4/54(7.41)	3/54(5.56)	0.959
Sepsis/pneumonia	3/54(5.56)	1/54(1.85)	0.363
Other serious adverse events			
Bleeding from banding ulcer	4/54(7.41)	0/54(0)	0.118
Peptic ulcer/gastritis	2/54(3.70)	2/54(3.70)	1.000
Urinary retention	0/54(0)	1/54(1.85)	1.000
Oesophageal stenosis	2/54(3.70)	0/54(0)	0.495
Deep venous thrombosis	1/54(1.85)	3/54(5.56)	0.618
TIPS, transjugular intrahepatic portosystemic shunt.			

The 6-, 12- and 18-month PFS rates after initial intervention were 23, 19 and 15%, respectively, in the endoscopic + β -blocker group and 91, 51 and 33%, respectively, in the TIPS group ($P < 0.001$, Table 2 and Fig. 1D). Univariable Cox regression analysis identified 4 factors associated with the risk of PFS. In the multivariate analysis, the endoscopic + β -blocker (HR 3.31; 95% CI: 1.89–5.80; $P < 0.001$) and Child-Pugh-Turcotte C (HR 1.98; 95% CI: 1.06–3.70; $P = 0.032$) were identified as independent progression factor of PFS (Table 4).

Changes in the Child–Pugh-Turcotte stages

One month after initial intervention, the distribution of the Child-Pugh-Turcotte improving, stabilizing, and worsening was 76, 9 and 15%, respectively, in the TIPS group and 12, 23 and 65%, respectively, in the endoscopic + β -blocker group (Table 2). The TIPS group had a significantly higher rate of postoperative Child-Pugh-Turcotte stage improving than that of the endoscopic + β -blocker group (76% [41/54] vs 15% [8/54]; $P < 0.001$, Table 2).

Safety Profile

During follow-up, 31 (31/52, 60%) patients in the endoscopic + β -blocker group and 24 (24/54, 44%; $P = 0.118$) in the TIPS group experienced at least one severe adverse event (AEs). The most common severe AEs in the endoscopic + β -blocker group were ascites (29%), hepatorenal syndrome (14%), HE (9.6%), liver failure (7.7%) and bleeding from banding ulcer (7.7%). In the TIPS group, HE (20%), liver failure (6%), deep venous thrombosis (6%), peptic ulcer/gastritis (4%) and hepatorenal syndrome (4%) were reported. There were no significant differences in the number of patients who experienced a specific AEs except ascites ($P < 0.001$) between both groups (Table 5).

The specific adverse event of TKI

No differences in TKI-related AEs were observed in either group (Supplementary Table 1). In the TIPS group, a total of 70 complications were observed in 36 patients. Three patients (8%) stopped using TKI due to intolerance. Seventy-six complications were observed in 39 patients in the endoscopic + β -blocker group. Three patients (8%) stopped using TKI due to intolerance.

Discussion

Before our study, few data on the impact of the use of TIPS for a second prophylaxis for rebleeding in advanced HCC patients with variceal bleeding. In most previous studies of primary and secondary prophylaxis[20–22], HCC was a criterion for exclusion, thus we were not in a position to fully understand whether strategies of treatment of portal hypertension in HCC-free patients do confer clinical benefits to advanced HCC patients who are receiving TKIs and presented with variceal bleeding. Therefore, well-designed prospective studies are needed to compare the efficacy and safety of TIPS with endoscopic + β -blocker for prevention of rebleeding in such patients.

All in all, our data stressed TIPS placement was superior to endoscopic + β -blocker therapy for secondary prevention of rebleeding, reduced risks of failure to control bleeding and incidence of discontinuation of TKI, with no serious procedure-related complications, which was translated into improved survival.

First, we focused on the feasibility and safety of TIPS implantation. Importantly, all patients enrolled in this study had PVTT, especially tumor thrombus in the main portal vein, and complete portal vein occlusion accounted for 52%. These patients are of particularly problematic as TIPS implantation may be associated with higher rates of

technical failure, liver failure and HE. In present study, after TIPS implantation, only one patient experienced HE of grade I. No TIPS-related liver failure occurred. A potential explanation for the feasibility results might be this study was markedly different from previous reported as following: (1) tumor thrombus in the trunk of the portal vein and its left or right branch, and the patent branches were successfully accessed with the conventional TIPS method[22]; (2) for tumor thrombus in the main portal vein and both its branches, We preferred the bifurcation of the portal vein as the puncture site, because the portal vein was enlarged due to expansion of the tumor thrombus; (3) in order to achieve long-term shunt patency, the tumor thrombus in the main portal vein should be completely covered; (4) contrast material is injected to determine whether access to a portal vein has been gained such as “grid-like outline”. Our findings confirm that the use of TIPS for the prevention of rebleeding is also suitable for HCC with portal hypertension, especially in advanced HCC patients who are receiving TKIs therapy and presented with variceal bleeding.

Second, we found that the use of TIPS was associated with a reduction in the number discontinuation of TKI therapy cases, which can translate into improved survival of advanced HCC. Notably, no differences in serious AEs or TKI treatment-related intolerance discontinuations cases were observed between the TIPS and endoscopic + β -blocker groups in our study. However, endoscopic + β -blocker group resulted in a higher incidence of discontinuation of TKIs therapy because of failure to control variceal bleeding or rebleeding. Therefore, it is important to prevent rebleeding in these patients and in this setting TIPS implantation may contribute to the possibility for subsequent TKI treatment.

Third, and even more important, this study confirmed that the use of TIPS for the prevention of rebleeding in advanced HCC patients with port hypertension was associated with a reduction in mortality. This beneficial effect on survival was observed even though rescue TIPS was used in patients in whom endoscopic + β -blocker treatment failed. Notably, mortality was very high among the patients who underwent the endoscopic + β -blocker treatment. Due to the lack of shunt function, the efficacy of endoscopic + β -blocker treatment for prevention of rebleeding in advanced HCC patients with portal hypertension is limited. In addition, the rebleeding leads to further deterioration of liver function, which is a more important reason for the high mortality after endoscopic + β -blocker treatment. These patients, in fact, the multiple endoscopic sessions required to curb the rebleeding risk can be not only unbearable for these frail patients, but can also delay TKIs treatment. However, TIPS can significantly improve child-Pugh-Turcotte staging by reducing intravascular pressure in the portal vein system, preventing rebleeding, and reducing ascites, and thus patients could better tolerate subsequent TKIs therapy, ultimately affecting survival through changes a higher adherence to TKIs therapy. The multivariate analysis revealed that endoscopic + β -blocker treatment options, rebleeding, discontinuation of TKIs therapy, Child-Pugh-Turcotte class C were independent negative prognostic factors for OS. After TIPS implantation, improved liver function should increase the likelihood of TKIs therapy. Hence, these findings provide the rationale to extend our current knowledge and practice by offering advanced HCC patients who are receiving TKIs therapy and presented with variceal bleeding can benefit from a preemptive (early) TIPS.

There were several limitations to the current study. First, we did not analyze the difference in length of hospital stay and cost between the two groups. Second, although our study was based on multiple tertiary hospitals, the number of analyzed patients was relatively small. Despite these limitations, our data are clinically meaningful, as our results offer the first comparison of the feasibility and clinical value of TIPS *versus* endoscopic + β -blocker treatment in patients of with particular issues, such TIPS implantation.

In conclusion, in advanced HCC patients who are receiving TKIs and presented with variceal bleeding, TIPS implantation is superior to endoscopic + β -blocker therapy for the prevention of rebleeding, reductions in the failure to control bleeding and mortality. Patients treated with TIPS implantation show improved the Child–Pugh–Turcotte stages and can better tolerate subsequent TKIs therapy, and translate into improved survival, thus TIPS is a feasible and effective management for the cirrhotic advanced HCC patients with portal hypertension.

Abbreviations

TIPS, transjugular intrahepatic portosystemic shunt; TKI, tyrosine kinase inhibitor; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; HE, hepatic encephalopathy; PVP, portal venous pressure; PPG, portosystemic pressure gradient.

Declarations

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Role in study

Concept and design: Yongping Yang, Fuquan Liu, Huiguo Ding. Data analysis: Yan Chen, Xuemei Ma, Xuefeng Zhang, Jing Lou, Linjing An, Yu Zhang, Xiujuan Chang, Zheng Dong, Wei Zhang, Huifang Kong, Jun Zhao. Writing and critical analysis: All.

Declaration of Interests

The authors declare no conflicts of interest.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approvals statement

This study protocol was reviewed and approved by the institution review board of Fifth Medical Center of Chinese PLA General Hospital, approval number [KY-2018-07-13-1]. The study was performed in accordance with the ethics standards of the institutional research committee and the recent Declaration of Helsinki, which conformed to the guidelines of the International Conference on Harmonization for Good Clinical Practice

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Figures

Figure 1

Kaplan-Meier analysis of freedom of variceal rebleeding, survival, progression freedom survival. (A) Probability of remaining free from significant variceal rebleeding. (B) Probability of variceal rebleeding after initial intervention upon receiving tyrosine kinase inhibitor. (C) Probability of survival after initial intervention (D) Probability of progression freedom survival after initial intervention.

TIPS: transjugular intrahepatic portosystemic shunt.

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