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Multicenter analysis of the use of transjugular intrahepatic portosystemic shunt (TIPS) for management of MPN-associated portal hypertension

Christopher R. Reilly, MD[1], **Daria V. Babushok, MD, PhD**[1,2], **Karlyn Martin, MD**[3], **Jerry L. Spivak, MD**[4], **Michael Streiff, MD**[4], **Ranjeeta Bahirwani, MD**[5], **Jeffrey Mondschein, MD**[6], **Brady Stein, MD**[3], **Alison Moliterno, MD**[4], and **Elizabeth O. Hexner, MD**[1,2]

[1]Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

[2]Abramson Cancer Center and the Division of Hematology & Oncology, Philadelphia, PA

[3]Division of Hematology and Oncology, Northwestern University, Chicago, IL

[4]Department of Medicine, Johns Hopkins Hospital, Baltimore, MD

[5]Liver Consultants of Texas, Baylor University Medical Center, Dallas, TX

[6]Department of Interventional Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA

Abstract

BCR-ABL1-negative myeloproliferative neoplasms (MPNs) are clonal stem cell disorders defined by proliferation of one or more myeloid lineages, and carry an increased risk of vascular events and progression to myelofibrosis and leukemia. Portal hypertension (pHTN) occurs in 7–18% of MPN patients via both thrombotic and nonthrombotic mechanisms and portends a poor prognosis. Transjugular intrahepatic portosystemic shunt (TIPS) has been used in the management of MPN-associated pHTN; however, data on long-term outcomes of TIPS in this setting is limited and the optimal management of medically refractory MPN-associated pHTN is not known. In order to assess the efficacy and long-term outcomes of TIPS in MPN-associated pHTN, we performed a retrospective analysis of 29 MPN patients who underwent TIPS at three academic medical centers between 1997 and 2016. The majority of patients experienced complete clinical resolution of pHTN and its clinical sequelae following TIPS. One, two, three, and four-year overall survival post-TIPS was 96.4%, 92.3%, 84.6%, and 71.4%, respectively. However, despite therapeutic

Corresponding author: Christopher R. Reilly, Address: 3400 Spruce Street, 100 Centrex Bldg, Philadelphia, PA 19104, christopher.reilly@uphs.upenn.edu, Phone: (407) 442-6243.

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Competing interests:
The authors declare that they have no competing financial interests.

Authors' contributions:
CR, DB and EH conceptualized the study. CR obtained regulatory approval for multi-institutional study. EH, DB, AM, BS, KM, JS provided and cared for study patients and contributed to data collection. CR, DB, AM, BS, and EH analyzed the data and revised the manuscript. CR wrote the manuscript. CR, DB, AM, BS, EH revised the manuscript. RB and JM provided expertise in hepatology and interventional radiology, respectively. All authors approved the final version of the manuscript.

anticoagulation, in-stent thrombosis occurred in 31.0% of patients after TIPS, necessitating additional interventions. In conclusion, TIPS can be an effective intervention for MPN-associated pHTN regardless of etiology. However, TIPS thrombosis is a frequent complication in the MPN population and indefinite anticoagulation post-TIPS should be considered.

Keywords

Myeloproliferative neoplasm; portal hypertension; Budd-Chiari syndrome; transjugular intrahepatic portosystemic shunt (TIPS

Introduction

BCR-ABL1-negative myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), are clonal stem cell disorders defined by proliferation of one or more myeloid lineages, and carry an increased risk of vascular events and variable progression to myelofibrosis and acute leukemia [1]. Over the last decade, MPNs have been increasingly characterized by distinct driver mutations that correlate with clinical features and confer prognostic significance. The *JAK2V617F* mutation occurs in 95% of PV and 50–60% of ET and PMF patients [2–5], and acquired mutations within *CALR* and *MPL* genes account for majority of *JAK2*-negative ET and PMF [6–8]. Intriguingly, multiple studies have consistently demonstrated a prominent role of *JAK2 V617F* in vascular risk generally and MPN-associated portal hypertension specifically, although the underlying pathobiologic basis is not well understood [11, 21].

Portal hypertension (pHTN) occurs in 7–18% of MPN patients and portends a poor prognosis [9–11]. The etiologies of pHTN in MPN involve both thrombotic and nonthrombotic mechanisms. The most common cause of MPN-associated pHTN is splanchnic vein thrombosis (SVT), which includes Budd-Chiari syndrome (BCS), portal vein thrombosis (PVT), mesenteric vein thrombosis, and splenic vein thrombosis. Extramedullary hematopoiesis (EMH) within the liver and spleen, a common feature of MPN, results in increased sinusoidal resistance and pressure within the portal circulation [11, 12]. Lastly, nodular regenerative hyperplasia (NRH), an under-recognized entity characterized by regenerative nodules in the absence of fibrosis, has been described in MPN patients with pHTN [13].

MPN-associated pHTN commonly presents with ascites, gastrointestinal varices, and, rarely, acute liver failure [11]. In contrast to cirrhotic pHTN, hepatic synthetic function is typically preserved in MPN-associated pHTN [13, 14]; however, this population similarly is at risk for refractory ascites and gastrointestinal bleeding [11]. Standard treatment of MPN-associated pHTN parallels treatment of cirrhotic pHTN, including diuretics, large-volume paracentesis, endoscopic variceal surveillance and ligation, and, rarely, orthotopic liver transplant. In cases of refractory pHTN, interventional approaches are used to reduce portal pressure. Traditional surgical portosystemic shunts were associated with high complication rates and periprocedural morbidity/mortality without an improvement in survival [15–17]. Over the last two decades, the less invasive option of transjugular intrahepatic portosystemic shunt (TIPS) procedure has largely supplanted the need for surgical shunts [16, 18]. TIPS

procedure involves the endovascular creation of an intrahepatic shunt between the inferior vena cava or hepatic veins and tributaries of the portal circulation to mitigate portal hypertension and its clinical sequelae. The utilization of TIPS in MPN-associated pHTN has been reported in case reports and case series [11, 19–21], but long-term outcomes in this patient population are limited. Indeed, the optimal management of MPN-associated pHTN is unknown and clinical management is largely inferred from management of cirrhotic pHTN. To evaluate the efficacy and long-term outcomes of TIPS in MPN, our group performed a retrospective analysis of TIPS outcomes for patients with MPN-associated portal hypertensions at three academic medical centers.

Methods

Patient population

We performed a multicenter retrospective study of long-term outcomes of TIPS for MPN-associated pHTN from 1997 to 2016. This time interval was selected to reflect current standard practices for MPN and portal hypertension as well as the more widespread adoption of polytetrafluoroethylene (PTFE)-covered stent-grafts. Data collection and analysis were performed with the approval of the Institutional Review Board of each of participating institutions [Johns Hopkins University (JHU), Northwestern University (NWU), University of Pennsylvania (Penn)]. Patients were identified for study inclusion in two ways: i) cross-referencing ICD-9 and10 diagnosis codes for both MPN-related diagnoses and pHTN-related diagnoses (see supplementary material for full list) and ii) through referral from other providers who treated MPN patients with TIPS. A manual chart review was performed to confirm study eligibility. Patients required: 1) a confirmed diagnosis of *BCR-ABL1*-negative MPN according to internationally established criteria [1] or confirmed isolated *JAK2V617F* mutation positivity with abdominal vein thrombosis and 2) a diagnosis of portal hypertension established by ultrasonographic evidence of portal flow reversal, presence of esophageal varices on endoscopy, direct measurement of hepatic venous pressure gradient (HVPG), and/or serum albumin-ascites gradient > 1.1 in the absence of cardiac dysfunction, and 3) TIPS procedure for medically refractory pHTN. Patients with other etiologies of pHTN, including alcoholic cirrhosis, chronic viral hepatitis, and nonalcoholic steatohepatitis (NASH) were excluded from the study. Etiology of pHTN was determined by review of clinical notes, imaging, and pathology specimens; the diagnosis of NRH was established by liver biopsy.

Study Outcomes

The primary study outcomes were clinical resolution of pHTN, rate of TIPS dysfunction, and overall survival (OS) post-TIPS. Clinical resolution was defined as the absence of esophageal varices on endoscopy and/or ascites on physical exam and resolution of acute liver failure. TIPS dysfunction was defined as TIPS thrombosis or stenosis resulting in clinical symptoms and/or requiring procedural intervention; asymptomatic ultrasound findings of altered flow velocities were not included. In all cases, TIPS thrombosis or stenosis were documented by Doppler ultrasound and confirmed by venography. For the OS analysis, patients with insufficient follow-up for each time interval were excluded (i.e. at least 12 months of follow-up was needed to be included in 1-year OS calculation).

Secondary outcomes were assessed from a single center and included: primary TIPS patency rate, which was measured from time of TIPS to diagnosis of the first TIPS dysfunction, and the ability to be removed from liver transplant list as a result of clinical improvement following TIPS. The incidence of other TIPS-related complications, such as development of hepatic encephalopathy (HE) and GI bleeding, was also assessed; HE was graded based on the West Haven Grading System and clinically significant GI bleeding was defined as requirement of blood transfusions and/or need for endoscopic intervention.

Statistical Analysis

Patient characteristics, clinical outcomes, and post-TIPS complications were analyzed and represented as percentages of the entire cohort or as incidence rates over the follow-up period. All continuous variables were reported as medians and ranges.

Results

Clinical Characteristics

Twenty-nine patients met eligibility criteria and were included in the study. The median age was 47 years (range 27–86) and 65.5% were women (Table 1). PV and PV-MF were the most common MPN subtypes (70.0%), followed by PMF (10.3%), ET (10.3%), and isolated *JAK2V617F* or *CALR* mutations in one patient each. Of note, three patients originally diagnosed with ET were subsequently identified as having PV prior to TIPS; additionally, another patient with isolated *JAK2V617F* mutation progressed to overt PV four years after TIPS. *JAK2V617F* mutation was present in 89.7% of patients, while *CALR* and *MPL* mutations were detected in one patient each.

BCS represented the predominant etiology of pHTN in 72.4% of patients; notably, two thirds of these patients were women with PV. Other SVT events (PVT, mesenteric vein thrombosis, and/or splenic vein thrombosis) occurred in 17.2% of patients and co-occurred with BCS in two patients. EMH was observed in 17.2% of patients and represented the primary cause of pHTN in PMF patients. Although no patients in our cohort had NRH in isolation, NRH was noted in two patients with concomitant EMH. The etiology of pHTN was multifactorial in 31% of patients (e.g. BCS with PVT or EMH with NRH).

The time interval between MPN diagnosis and the development of pHTN varied by MPN subtype. For patients with myelofibrosis (PMF and PV-MF), pHTN was identified after a median interval of 36 months following MPN diagnosis, whereas the majority of PV and ET patients (70%) were diagnosed concurrently with MPN and pHTN. Indications for TIPS included refractory ascites (86%), esophageal varices (51.7%), intestinal ischemia due to mesenteric vein thrombosis (6.9%), fulminant liver failure (6.9%), and recurrent hydrothorax in one patient. MPN-specific treatments prior to and following TIPS included hydroxyurea (44.8%), phlebotomy (37.9%), aspirin (34.5%), ruxolitinib (13.8%), and interferon-alpha (3.4%); post-TIPS, two patients underwent allogeneic stem cell transplant for AML transformation and one PV-MF patient received imatinib after developing CML. Long-term anticoagulation included vitamin-K antagonist (VKA) (69%), VKA and aspirin (6.9%), low-molecular weight heparin (17.2%), and fondaparinux (17.2%). In most instances,

development of TIPS thrombosis or HIT prompted a change to an alternative anticoagulant. Four patients (13.8%) did not receive anticoagulation following TIPS due to the treating clinician preference because of thrombocytopenia and perceived high bleeding risk.

Efficacy of TIPS for MPN-associated pHTN

All patients demonstrated immediate reduction of portal pressures following TIPS insertion with a goal HVPG of less than 10–12mmHg. The majority of patients experienced complete resolution of ascites (96.2%) and varices (93.3%) after TIPS; one patient with refractory ascites after TIPS was found to have peritoneal EMH. One- and two-year primary TIPS patency rates were 89% and 78% of evaluable patients, respectively; all but three patients received PFTE-covered stents. One, two, three, and four-year overall survival post-TIPS was 96.4%, 92.5%, 85.2%, and 72.3%, respectively. Of the eight patients listed for liver transplant prior to TIPS, only two patients ultimately required transplant, and the remaining six patients were able to come off transplant list due to improved ascites and hepatic function.

Complications

Sixty-nine percent of patients experienced TIPS-related complications. TIPS dysfunction occurred in 37.9% of evaluable patients over a median follow up of 48 months (range 3 to 228); one third of these patients required subsequent shunt revision at a median interval of 22.3 months (range 10–34 months). Overall, the most common complication was TIPS thrombosis, which occurred in 31.0% of patients. TIPS thrombosis developed predominantly in patients with PV (77.8% of all events) and 40.0% of all PV patients in our cohort experienced TIPS thrombosis. Notably, all TIPS thrombosis developed in patients with BCS and despite therapeutic anticoagulation before and after the procedure. Endovascular management of thrombosis and/or stenosis involved a combination of angioplasty, mechanical thrombectomy, and stent extension depending on luminal patency, location of occlusion, and clot burden in each patient. Low-grade HE following TIPS occurred in 20.7% of patients. Symptoms were controlled with medical management and no patients required TIPS reversal for refractory encephalopathy. Other complications included heparin-induced thrombocytopenia (HIT; 20.7%), GI bleed in the setting of TIPS stenosis (6.9%), and periprocedural NSTEMI in one patient that did not require further intervention. After a median follow-up of 48 months, there were seven deaths and none were attributable to TIPS complications or dysfunction.

Discussion

Our study represents the largest cohort to date of MPN patients treated with TIPS for medically refractory pHTN due to both thrombotic and nonthrombotic causes. TIPS procedure demonstrated substantial clinical efficacy, primary patency rates, and overall survival in our MPN cohort: including resolution of ascites and/or varices in over 90% of patients, primary 1-year patency rate of 89%, and three-year overall survival greater than 85%. We also observed that TIPS is associated with a high rate of manageable complications that must be weighed against the intended clinical benefit.

The widespread adoption of PTFE-covered stents has greatly improved long-term TIPS patency rates compared to traditional bare metal stents [15]. However, TIPS dysfunction remains the most significant long-term complication of the procedure [22]. Compared to cirrhotic patients, idiopathic BCS patients (~40–50% MPN prevalence) have a higher incidence of TIPS dysfunction (42 vs. 13%), presumably due to the systemic hypercoaguable state of MPN [23–26]. In a study of BCS patients, MPN diagnosis was an independent risk factor of TIPS dysfunction [30]; however, a larger study found that TIPS dysfunction occurred in 41% of patients with no difference in outcomes for patients with or without MPN [16]. In our study, the overall incidence of TIPS dysfunction was 37.9% and data from a single center demonstrated 1- and 2-year primary patency rates with PFTE-covered stents of 89% and 78%, respectively. The primary TIPS patency rate in our study was higher than previous studies of BCS patient with reported 1-year patency rates between 56%–80% with PTFE-coated stents [27, 28]. While the utility of TIPS has been established in BCS, there is little published data of TIPS used for nonthrombotic pHTN [19, 24, 25]. Previously, a small case series of 24 patients with NRH demonstrated clinical resolution of variceal bleeding and ascites in ten patients who underwent TIPS [29], and another case series reported successful TIPS in two patients with PMF and EMH [19, 30]. Our results contribute to the literature and suggest a promising role of TIPS for nonthrombotic etiologies of MPN-associated pHTN.

Overall survival following TIPS was high in our group, with one, two and three-year overall survival post-TIPS of 96.4%, 92.5%, and 85.2%, respectively. This closely mirrors the findings of a recent systematic review that found BCS-TIPS patients had a 1-year cumulative survival rate of 80–100% and a 5-year cumulative of 74–78% [31]. Of note, the incidence of hepatic encephalopathy in our cohort was low; this may reflect greater intact hepatic synthetic function compared to cirrhotic patients receiving TIPS. The long-term survival of these patients underscores the need to longitudinally monitor for TIPS dysfunction and determine optimal prevention and management of complications.

Currently, indefinite anticoagulation is recommended for MPN patients who receive TIPS to prevent recurrent thrombotic events given the systemic hypercoagulability of the disease [25, 32]. In a study of 181 MPN patients with SVT, De Stefano et al. demonstrated that even despite anticoagulation, there is a high rate of recurrent thrombosis in MPN, with independent predictors of recurrent thrombosis including history of BCS, prior thrombosis, splenomegaly, and leukocytosis [32]. The risk of recurrent thrombosis was diminished with the use of VKA but the combination of aspirin and VKA did not further reduce this risk [32]. It is still not known if MPN-specific therapy, in addition to anticoagulation, influences risk of developing or severity of MPN-associated pHTN. While a recent meta-analysis of PV and PMF patients showed a reduced risk of thrombosis in patients treated with ruxolitinib [33], it is unknown whether ruxolitinib will reduce the risk of SVT. A prospective phase 2 trial of ruxolitinib in MPN patients with SVT observed a significant reduction in spleen size but did not produce an appreciable effect on esophageal varices or ultrasonagraphic indices of pHTN [34]. In our cohort, cytoreductive therapy (including ruxolitinib) was prevalent and did not appear to affect outcomes but the small sample limits correlative analysis. Optimally, biomarkers to predict thrombotic outcomes and larger prospective studies are needed to determine the optimal MPN therapy for these patients. An ongoing clinical trial investigating

pegylated interferon for salvage therapy of high-risk MPN patients with splanchnic vein thrombosis may provide more insight regarding this question [ClinicalTrials.gov - NCT01259817].

Several studies have demonstrated a strong association between *JAK2*-positive MPN and SVT [11, 32, 35], and this correlation was recapitulated in our cohort. A large meta-analysis by Smalberg et al. reported a MPN prevalence in idiopathic BCS and PVT of 41% and 31.5%, respectively [35]. Similarly in our study, JAK2 positivity was found in 89.7% of patients. MPN subtype appears to influence risk of SVT, as Yan et al. demonstrated a significantly higher incidence of SVT in PV or post-PV MF compared to other MPNs (76% v. 27%) [11]. Similarly, SVT occurred with greater frequency in PV and PV-MF compared to other MPN subtypes in our cohort.

Despite a strong correlation, the specific mechanism underlying the *JAK2V617F* mutation and development of MPN-associated pHTN is not known. One possible explanation is that *JAK2* mutations are acquired in a pluripotent stem cell with the capacity to contribute to hematopoietic and endothelial lineages, which may contribute to thrombogenicity; this is supported by patient samples demonstrating the presence of *JAK2* V617F mutation in hepatic endothelial cell progenitors [36, 37]. Intriguingly, while PV is highly associated with SVT, one study found that the risk of recurrent thrombosis was independent of MPN subtype or *JAK2V617F* mutation positivity [32]. Other less common MPN driver mutations, such as *CALR, MPL* and *JAK2* exon 12 have not exhibited a consistent correlation with SVT [35, 38, 39]; however, one patient in our cohort had an isolated *CALR* mutation and BCS, indicating a tight but incomplete correlation between *JAK2V617F* and MPN-associated pHTN. Lastly, the incidence of HIT in our cohort was surprisingly high (20.7%), and HIT occurring in MPN patients has rarely been reported [40, 41]. It is unclear why our rate of HIT was high, and this potential association should be explored in future studies given the relevant implications for long-term anticoagulation in this population.

Limitations of our study are the relatively small cohort size and the retrospective nature of the analysis. However, our study focuses on a subset of patients with rare hematologic neoplasms, and our results reflect the longitudinal experience of three academic centers over the last two decades. Future multi-center, prospective studies are needed to better characterize which subsets of MPN-associated pHTN are most likely to benefit from TIPS and to establish the optimal management of TIPS dysfunction in this population.

In conclusion, our results indicate that TIPS is a well-tolerated and effective treatment of MPN-associated pHTN regardless of MPN subtype or etiology of pHTN. The high incidence of TIPS thrombosis in patients with PV and BCS supports long-term anticoagulation and close clinical monitoring for evidence of TIPS dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of abbreviations

PV	polycythemia vera
PV-MF	post-PV myelofibrosis
PMF	primary myelofibrosis
ET	essential thrombocythemia
BCS	Budd-Chiari syndrome
PVT	portal vein thrombosis
SVT	splanchnic vein thrombosis
EMH	extramedullary hematopoiesis
NRH	nodular regenerative hyperplasia
EV	esophageal varices
LMWH	low-molecular weight heparin.

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Table 1

Demographic and Clinical Patient Characteristics

Clinical Characteristics		
Number of patients, n (%)	29	(100%)
Age, years, median (range)	47	(range 27–86)
Gender, n (female/male)	19/10	
MPN subtype, n (%)		
PV/PV-MF	20	(70.0%)
PMF	3	(10.3%)
ET	3	(10.3%)
Isolated JAK2/CALR mutation	2	(6.9%)
Driver mutation, n (%)		
JAK2V617F	26	(89.7%)
CALR	1	(3.4%)
MPL	1	(3.4%) *
MPN Therapy, n (%)		
Phlebotomy	11	(37.9%)
Aspirin	10	(34.5%)
Hydroxyurea	13	(44.8%)
Ruxolitinib	4	(13.8%)
Interferon alpha	1	(3.4%)
Etiology of portal hypertension, n (%)		
BCS	21	(72.4%)
PVT	6	(20.7%)
Other SVT	5	(17.2%)
EMH	5	(17.2%)
NRH	2	(6.9%)
Multifactorial	9	(31.0%)
TIPS indication, n (%)		
Ascites	25	(86.0%)
Esophageal varices	15	(51.7%)
Ascites and esophageal varices	13	(44.8%)
Intestinal ischemia	2	(6.9%)
Liver failure	2	(6.9%)
Hepatic hydrothorax	1	(3.4%)
Anticoagulation, n (%)		
Coumadin	20	(69.0%)
Low-molecular weight heparin	5	(17.2%)
Fondaparinux	5	(17.2%)
None	4	(13.8%)

Abbreviations: PV, polycythemia vera; PV-MF, post-PV myelofibrosis, PMF, primary myelofibrosis; ET, essential thrombocythemia; BCS, Budd-Chiari syndrome; PVT, portal vein thrombosis; SVT, splanchnic vein thrombosis; EMH, extramedullary hematopoiesis; NRH, nodular regenerative hyperplasia. n, number of patients with the listed clinical characteristic.

* Patient also had concurrent *JAK2V617* mutation.

Table 2

Post-TIPS Outcomes

Clinical Resolution, n (%)		
Ascites	24	(96.2%)
Esophageal varices	15	(93.3%)
Removed from transplant list *	6	(75.0%)
Overall Survival		
1-year		96.4%
2-year		92.3%
3-year		84.6%
4-year		71.4%
TIPS patency ∞		
1-year		89%
2-year		78%

* Patients had clinical improvement and no longer required transplant

∞ Data obtained from a single institution with 14 patients; one third required shunt revision at median of 22.3 months.

Table 3

Post-TIPS Complications

Complications	Patient Number, n (%)
None	7 (24.1%)
TIPS thrombosis	9 (31.0%)
TIPS stenosis	5 (17.2%)
Hepatic encephalopathy	6 (20.7%)
Grade 1	3
Grade 2	2
Grade 3 or 4	1
Heparin-induced thrombocytopenia	6 (20.7%)
GI bleed	2 (6.9%)
NSTEMI	1