Use of Paclitaxel-Coated Balloon Catheter Dilation to Reduce In-Stent Restenosis in Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Anwendung Paclitaxel-beschichteter Ballonkatheter im transjugulären intrahepatischen portosystemischen Shunt (TIPS) zur Reduktion der In-Stent-Restenose

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Key words

- portosystemic shunt
- transjugular intrahepatic balloon angioplasty
- paclitaxel

Zusammenfassung

Ziel: Paclitaxel-beschichtete Ballonkatheter (PCB) vermindern die Neointimaproliferation in Arterien. Das Ziel dieser retrospektiven Analyse war es, den Effekt von PCB in In-Stent-Restenosen durch Pseudointimahyperplasie nach transjugulärem intrahepatischen portosystemischen Shunt (TIPS) zu untersuchen.

Material and Methoden: Sechs Patienten (mittleres Alter, 65 ± 10 Jahre) mit rezidivierenden In-Stent-Stenosen im TIPS (5 „Bare-Metal-Stents“, 1 ummantelte Endoprothese) erhielten eine einzelne perkutane transluminale Angioplastie (PTA) mit PCB ($3 \mu\text{g}$ Paclitaxel/ mm^2). Das postinterventionelle Outcome und die Offenheitsrate wurden innerhalb des Patientenkollektives mit vorangegangenen unbeschichteten PTAs (POBA) verglichen. Während einer Zeitperiode von 2 Jahren wurden die Patienten im Abstand von 6 Monaten klinisch und angiografisch kontrolliert. Die kürzesten In-Stent-Lumendurchmesser (MLD) und das „Late lumen loss“ (LLL) wurden bestimmt. Residuelles Paclitaxel wurde auf den Ballonkathetern, den Schleusen und in venösen Blutproben (0–24 Stunden) analysiert.

Ergebnisse: PCB verminderte die Notwendigkeit für klinisch indizierte, Re-PTAs (POBA, 53 % der Angiografien; Paclitaxel PTA, 19 %, $P=0,014$). Das LLL der Stenosen war nach POBA größer ($2,4 \pm 1,5 \text{ mm}/28 \pm 18 \%$) im Vergleich zu den PTAs mit PCB ($0,5 \pm 0,8 \text{ mm}/7 \pm 11 \%$, $P=0,029$). $28 \pm 9 \%$ der applizierten Paclitaxel-Konzentration wurde residuell auf den Oberflächen der Ballonkatheter und $0,2 \pm 0,1 \%$ auf den Oberflächen der Schleusen beobachtet. Paclitaxel-Plasmakonzentrationen lagen innerhalb der ersten 24 Stunden nach den Interventionen unterhalb der Detektionsgrenze. Es wurden keine Paclitaxel assoziierten Nebenwirkungen beobachtet.

Schlussfolgerung: Die singuläre PTA mit einem Paclitaxel-beschichteten Ballon führt zu einer verbesserten sekundären Offenheitsrate bei TIPS-

Abstract

Purpose: Paclitaxel-coated balloons (PCB) inhibit neointimal proliferation in arteries. The purpose of this retrospective analysis was to investigate the effect of PCB in in-stent restenosis after transjugular intrahepatic portosystemic shunt (TIPS) in patients with cirrhotic liver disease.

Materials and Methods: Six patients (mean age: 65 ± 10 years) with recurrent in-stent restenoses in TIPS (5 bare stents, 1 covered stent) underwent a single percutaneous transluminal angioplasty (PTA) with PCB ($3 \mu\text{g}$ paclitaxel/ mm^2). Post-interventional outcome and patency were compared with those of prior plain optimal balloon angioplasty (POBA) in the same patients. During a two-year follow-up period, all patients underwent angiographic examinations at 6-month intervals. In-stent minimal lumen diameter (MLD) and late lumen loss (LLL) were assessed. Paclitaxel residues on balloon and sheath surfaces as well as venous plasma concentrations (0–24 hours) were analyzed.

Results: PCB decreased the need for clinically driven repeat PTA (POBA: 53 % of angiographic examinations; paclitaxel PTA: 19 %; $P=0.014$). LLL/diameter stenosis was higher after POBA ($2.4 \pm 1.5 \text{ mm}/28 \pm 18 \%$) than after PCB ($0.5 \pm 0.8 \text{ mm}/7 \pm 11 \%$, $P=0.029$). Residual paclitaxel on balloons was $28 \pm 9 \%$ of dose and $0.2 \pm 0.1 \%$ on sheath surfaces. Paclitaxel plasma concentrations were below detectable levels throughout the first 24 hours after the interventions in all patients. The procedure was well tolerated and no clinical side effects attributable to paclitaxel were observed.

Conclusion: In patients with recurrent in-stent stenoses, a single PTA with PCB resulted in a prolonged secondary patency due to pseudointimahyperplasia without a systemic effect of paclitaxel.

Key points:

- ▶ Intimahyperplasia is a common reason for long-time TIPS dysfunction

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Bibliography

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Dysfunktion durch Pseudointimahyperplasie ohne dabei Paclitaxel bedingte systemische Effekte zu verursachen.

Kernaussagen:

- ▶ Intimahyperplasie ist Ursache für langfristige Shunt-Dysfunktionen.
- ▶ Erstmaliger Bericht über lokale Paclitaxel-Applikation bei Patienten mit rezidivierenden Stenosen im TIPS zur Reduktion der Pseudointimahyperplasie.
- ▶ Eine PTA mit PCB verlängert die sekundäre Offenheitsrate des TIPS im Vergleich zur normalen PTA.

- ▶ First-in-man local paclitaxel application in TIPS patients with recurrent in-stent stenoses
- ▶ PTA with PCB resulted in a prolonged secondary patency compared to POBA
- ▶ No systemic effects of Paclitaxel were detected

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Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is the therapeutic method of choice to reduce the complications of portal hypertension. Because of its feasibility and low mortality rate, TIPS has become a clinical standard [1–3]. Some investigators have pointed out that shunt dysfunction occurs in 50–85% of patients within the first year of TIPS insertion in patients with bare metal stents [4]. Early TIPS dysfunction (within 30 days) is most commonly caused by thrombosis linked to perioperative trauma and bile leak, while in-stent intimal pseudohyperplasia is a frequent cause of long-term TIPS dysfunction [1, 5, 6], which can lead to frequent re-interventions in a subgroup of TIPS patients with a long clinical follow-up and TIPS patency.

Plain optimal balloon angioplasty (POBA) is an established method for vascular in-stent dilation and functional recovery. Paclitaxel coated balloons (PCB) are used in arteries and dialysis shunts to prospectively inhibit intima proliferation to prevent recurrent stenosis and therefore optimize secondary patency after PTA [7–10]. This is the first-in-man use of PCB for patients with cirrhotic liver disease and recurrent TIPS in-stent stenoses. In-stent patency after treatment was evaluated as well as the short-term tolerability, the residual drug content of used balloon catheters and sheaths, and systemic venous plasma paclitaxel concentrations.

Materials and Methods

Patients

All patients gave informed consent to this compassionate use of treatment. After TIPS insertions, patients in our hospital are monitored with clinical examination as well as ultrasound and invasive angiographic follow-up examinations every 6 months, according to our hospital standard. This analysis included six patients (3 men, 3 women; mean age: 65 ± 10 years) who were diagnosed with recurrent TIPS dysfunction due to in-stent restenoses. Restenoses occurred during a mean period of 76 ± 32 months (mean: 7 ± 3 restenoses per patient) after implantation of TIPS. All patients had a clinical indication for PTA and were treated between January 2010 and December 2012. The mean TIPS duration between stent insertion and the first uncoated PTA was 18 ± 7 months (Table 1). Following TIPS, all patients underwent angiographic examination at 6-month intervals, according to our in house follow-up protocol, and additional examination if there was a clinical need.

Shunt dysfunction was clinically defined as a portosystemic pressure gradient (PPG) exceeding 15 mmHg and in-stent restenosis and/or in-stent lumen narrowing to less than 50% of the stent diameter combined with new ascites or rebleeding. Mean PPG was determined before and after the interventions.

Patients with tumor disease were not treated with PCB. Results of PCB treatment were compared on an intra-patient basis with the results of earlier treatments with uncoated balloons (the latter thus served as controls).

Table 1 Individual patient data.

patient	age ¹	gender	initial stent type	covering	TIPS-duration before paclitaxel (months)	number of previous stenoses (n)	first PTA after TIPS insertion (months)	in-stent stenosis side
1	46	male	Viatorr (10/60 mm, W.L. Gore)	covered	72	9	22	hepatic vein
2	73	female	Luminexx (10/60 mm, C.R. Bard)	non-covered	84	9	12	hepatic vein
3	72	male	Memotherm (10/50 mm, 10/70 mm, C.R. Bard) ²	non-covered	90	8	11	hepatic vein
4	70	female	Memotherm (10 × 60 mm, C.R. Bard)	non-covered	102	6	25	hepatic vein
5	65	female	Memotherm (10 × 60 mm, C.R. Bard)	non-covered	92	8	25	portal vein
6	66	male	Luminexx (10/50 mm, 10/80 mm, C.R. Bard) ²	non-covered	13	1	13	portal vein
mean ± SD	65 ± 10				76 ± 32	7 ± 3	18 ± 7	

¹ Age at time of PTA with paclitaxel-coated balloon catheter.

² Patients 3 and 6 received two overlapping stents.

Fig. 1 Images of transjugular intrahepatic portosystemic shunt (TIPS) in one patient before and after catheterization with a paclitaxel-coated balloon (PCB) catheter. **A** Decreased in-stent minimum lumen diameter (MLD) before paclitaxel PTA on day 0 after recurrent stenosis. **B** Paclitaxel PTA. **C** Increased in-stent MLD after PCB treatment. **D–F** Follow-up images obtained 6–18 months after treatment show nearly the same in-stent MLD at all follow-up times. The arrow indicates the in-stent lumen reduction, which did not increase over the 24-month follow-up period. Asterisk = portal vein; Bar = 10 mm; PTA = percutaneous transluminal angioplasty.

Abb. 1 Abbildungen des transjugulären intrahepatischen Shunts des selben Patienten vor und nach Katheterisierung mit Paclitaxel-beschichteten Ballonkathetern (PCB). **A** Abnahme des minimalen In-Stent-Lumendurchmessers (MLD) vor Paclitaxel-PTA an Tag 0 nach vorangegangenen rezidivierenden Stenosen. **B** Paclitaxel-PTA. **C** Erhöhter In-Stent-MLD nach PCB-Behandlung. **D–F** Die Abbildung der angiografischen Nachsorge im Zeitraum von 6–18 Monaten nach Behandlung zeigen nahezu die gleichen MLD. Die Pfeile kennzeichnen die In-Stent-Lumen-Reduktionen, bei welchen kein Anstieg über einen Verlauf von 24 Monaten zu beobachten war. Stern = Portalvene; Balken = 10 mm; PTA = Perkutane transluminale Angioplastie.

Initial TIPS Insertion

Initial TIPS insertion was performed under combined fluoroscopic and sonographic guidance in all patients. Six patients received eight initial stents: Luminexx (C.R. Bard, Murray Hill, USA) 10/50 mm (n=1), 10/60 mm (n=1), and 10/80 mm (n=1); Memo-therm (C.R. Bard, Murray Hill, USA) 10/50 mm (n=1), 10/60 mm (n=2), and 10/70 mm (n=1). In two patients there were two overlapping stents. One patient received a 10/60 mm Viatorr endoprosthesis (W.L. Gore, Flagstaff, USA). In all patients, the underlying liver disease was alcoholic cirrhosis. Individual data are shown in **Table 1**.

Procedure Protocol

All invasive interventions were performed under systemic pain medication (5 mg pitriamid) and local anesthesia, according to the

hospital standard. After exclusion of any coagulation disorders, a single dose of 5000 IU heparin was administered intravenously before angioplasty.

Conventional Angioplasty in Restenosis

A transjugular, sheath-mediated angioplasty balloon catheter (Paseo-35, Biotronik, Germany; balloon dimensions: 10/40 mm) was placed in the portocaval stent according to the identified stenosis and inflated with a constant pressure of 7 atm that was maintained for 3 minutes. All patients repeatedly received POBA with uncoated balloon catheters before PCB angioplasty for TIPS restenosis.

PCB Angioplasty in Restenosis

Technical insertion of PCB was performed as described for conventional PTA. Paclitaxel was passively transferred into the seg-

ment of stenosis during inflation of the PTA balloons (Admiral™, Invatec S.p.A, Italy; balloon dimensions: 10/40 mm). The angioplasty balloons were inflated with a constant pressure of 7 atm that was maintained for 3 minutes.

During the post-procedural hospital stay, all patients were observed and monitored for at least 24 hours after the procedure.

Paclitaxel-Coated Balloon Catheters and Paclitaxel Analysis

The balloon surfaces of sterile PTA balloon catheters were coated with paclitaxel ($3 \mu\text{g}/\text{mm}^2$) in a hydrophilic matrix by the hospital pharmacy as described before [11]. After balloon dilation, residual paclitaxel on the balloons and sheaths was analyzed by high-performance liquid chromatography (HPLC).

The difference between the pre- and post-interventional amounts of paclitaxel on the balloons was defined as the in vivo dose. Systemic paclitaxel exposure was assessed in venous blood samples before treatment and 0.5, 4, and 24 hours after the intervention. The venous blood samples were analyzed for residual paclitaxel by HPLC. The limit of paclitaxel detection was 5 ng/ml for all samples.

Follow-up Protocol

The standard follow-up protocol after PCB included clinical evaluation and ultrasound imaging as well as invasive pressure monitoring and angiographic imaging every six months during a two-year follow-up period after single PCB. In any case of recurrence of shunt dysfunction with clinical signs of portal hypertension after PCB, POBA with uncoated balloon catheters was performed. The follow-up endpoint during angiographic examination was the first recurrent need for a further PTA (POBA) after a single PCB-PTA.

In-stent minimal lumen diameter (MLD) at the side of stenosis was measured on a commercially available workstation. The difference in MLD between two successive angiographic examinations was given as late lumen loss (percentage decrease in MLD). In cases where a PTA (POBA or PCB) was performed, the MLD after PTA was taken as the baseline value for the following time interval. Mean late lumen loss (LLL), defined as MLD at the last assessment minus MLD at the following assessment in mm (or the difference in percentage of diameter stenosis) for several time intervals was calculated for each patient.

The percentage of angiographic examinations that needed a PTA was calculated for the period before (period of recurrent stenosis following POBA) and after a single paclitaxel PTA. The two percentages were compared with each other.

Statistics

Numerical values are given as means with standard deviations. Statistical analysis was performed by a two-sided Student's t test using Graph Pad Prism 6.0 for Macintosh. Binary and categorical variables such as clinical outcomes were compared using Fisher's exact test. A P value below 0.05 was considered statistically significant.

Results

During a 16-month period (from January 2012 until October 2013), 6 of 48 patients with recurrent re-stenosis and concomitant recurrent ascites were treated with PCB. A mean of 7 ± 3 restenoses

treated with POBA per patient (range 1–9) were observed before considering PCB.

The mean TIPS duration between stent insertion and the first POBA was 18 ± 7 months. The mean duration of re-intervention with a POBA was 6 ± 0.4 months. A POBA was indicated for every other angiographic follow-up examination (41 of 77, 53%).

PCB-PTA was performed 76 ± 32 months after TIPS insertion (Table 1). In-stent stenosis occurred at the proximal (venous) segment in four patients and at the distal (portal) segment of the stent in two patients (Fig. 1). In an intra-individual correlation, late lumen loss was higher after POBA ($2.4 \pm 1.5 \text{ mm}/28 \pm 18\%$) than after PCB-PTA ($0.5 \pm 0.8 \text{ mm}/7 \pm 11\%$, $P=0.029$) (Fig. 2). After PTA with a PCB, the percentage of angiographic examinations with the need of PTA decreased to 19% (3 of 16, $P=0.014$) (Fig. 3). In two patients, restenosis was diagnosed after six months. Four of six patients showed no relevant restenosis up to 18 months after PCB PTA, and two of them showed no relevant restenosis after 24 months post intervention. One of these patients received a liver transplantation (not attributable to paclitaxel) after 18 months of follow-up without occurrence of restenosis. One patient with recurrent re-stenosis after PCB was treated with an endograft (stent in stent, Viatorr, 10/60 mm, W.L. Gore, Flagstaff, USA) after 20 months (Fig. 4). Detailed individual data are presented in Table 2.

Residual paclitaxel on the balloons was $28 \pm 9\%$ of the original $3 \mu\text{g}$ paclitaxel/ mm^2 (0.8 ± 0.3 paclitaxel/ mm^2) and $0.2 \pm 0.1\%$ of the calculated dose was found in the extracts of the sheaths (0.008 ± 0.003 paclitaxel/ mm^2). The corresponding mean in vivo paclitaxel dose was $72 \pm 9\%$ of the total dose on the balloons. Paclitaxel levels were below 5 ng/ml in all venous blood samples after treatment. The procedure was well tolerated and no clinical side effects attributable to paclitaxel were observed.

Fig. 2 In-stent minimal lumen diameter (MLD) is affected by local paclitaxel administration. Late lumen loss was higher after plain optimal balloon angioplasty (POBA) with uncoated balloons; * $P=0.029$, paclitaxel-coated balloon (PCB) vs. POBA.

Abb. 2 Der minimale In-Stent-Lumendurchmesser (MLD) wird durch die lokale Paclitaxel-Applikation beeinflusst. Das Late lumen loss war nach konventioneller PTA mit unbeschichteten Ballonen (POBA) erhöht; * $P=0,029$, Paclitaxel-beschichtete PTA (PCB) vs. POBA.

Discussion

This retrospective analysis investigates the compassionate first-in-man use of PCB in the treatment of recurrent TIPS dysfunction due to multiple restenoses in six patients. Our results suggest that secondary patency of TIPS is higher after treatment with paclitaxel-coated balloons compared with uncoated balloon angioplasty. Thromboses and bile leaks were identified as main causes for early TIPS dysfunction. In contrast, one reason for long-term TIPS dysfunction is the unpredictable patency of the shunts due to pseudointimal hyperplasia within the parenchymal tract or within the outflow hepatic vein. Histopathologic investigations of in-stent neolumina in the TIPS tract have revealed the development of an

organized in-stent cell layer that is different from the lining of a normal vessel wall. Continuous lining of the inner stent with mature endothelial cells of unknown origin has been reported [12, 13]. Stimulation of pseudointima formation through migration and proliferation of smooth muscle cells in the middle layer [14], lined by hepatic sinusoidal cells [14], and increased collagen type I and II secretion by TIPS cells have been found in human specimens of TIPS patients [13]. Proliferation of smooth muscle cells has also been identified as a major cause of TIPS stenosis in an animal model [15]. Another group has described proliferation of myofibroblasts and fibrin within the neolumen [12]. Paclitaxel is known to have an effect on intimal cell proliferation and also inhibits cell migration in a concentration-dependent manner [16]. Therefore, it might have an effect which is not limited directly to the place of application [17]. The artificial connection of two vessel systems with differences in resistance causes turbulences and shear stress, which could play a complementary role in focal pseudointimal hyperplasia. Electron-microscopic findings suggesting that endothelial cell arrangement depends on the direction of blood flow [12] are in line with this hypothesis.

Growing knowledge about stent material characteristics and their effects has led to several studies investigating modified stent surfaces customized to avoid shunt dysfunction. The first use of such a modified, polytetrafluoroethylene (PTFE)-covered stent in humans was reported in 1999. Various studies found a better patency rate and clinical outcome compared with conventional bare metal stents [3, 18–20]. These data are unambiguous; however, restenosis occurs with both types of stent. PTFE-covered endoprostheses show stenoses in the hepatic venous outflow tract and at the junction between the non-covered and covered segments of the stent graft [19, 21]. Venous outflow stenosis is one of the most frequent locations of TIPS stenosis, especially if the stent is not reaching the confluence of the hepatic veins. The outflow hepatic veins can shrink diffusely to half of their diameter after TIPS implantation [4]. In our patients no venous outflow tract stenoses were observed.

Additional studies to analyze the effect of local paclitaxel delivery to the hepatic venous outflow tract would be helpful, as paclitaxel proved to show positive effects on stenosis in arteriovenous fistulas compared to POBA [8]. Other strategies to increase TIPS

Fig. 3 Local paclitaxel delivery from coated balloons decreased the need for clinically driven repeated percutaneous transluminal angioplasty (PTA) compared with plain optimal balloon angioplasty (POBA); * $P = 0.014$, paclitaxel-coated balloon (PCB) vs. POBA.

Abb. 3 Eine lokale Paclitaxelapplikation durch beschichtete Ballone (PCB) verringert die Notwendigkeit für weitere Angioplastien verglichen mit der konventionellen PTA (POBA); * $P = 0,014$, PCB vs. POBA.

Fig. 4 Months without repeat PTA (percutaneous transluminal angioplasty) after treatment with paclitaxel-coated balloon (PCB). Day 0 corresponds to a single PCB treatment. No need to repeat PTA in patients 2, 4, and 6. Patient 6 received a liver transplantation after 18 months. Patient 5 was treated with an endograft (stent in stent) after 20 months. Asterisk = first PTA (POBA) after PCB; PTA = percutaneous transluminal angioplasty; PCB = paclitaxel-coated balloon.

Abb. 4 Monate ohne eine erneute PTA (perkutane transluminale Angioplastie) nach Behandlung mit Paclitaxel-beschichteten Ballonen (PCB). Tag 0 entspricht einer einmaligen PCB. Bei den Patienten 2, 4 und 6 bestand keine Notwendigkeit einer repetierten PTA. Der Patient 6 erhielt eine Lebertransplantation nach 18 Monaten. Der Patient 5 erhielt nach 20 Monaten einen weiteren Stent (Stent in Stent). Stern = Erste PTA (POBA) nach PCB; PTA = Perkutane transluminale Angioplastie; PCB = Paclitaxel beschichteter Ballon.

Table 2 Individual patient in-stent MLD and LLL before and after paclitaxel-coated balloon PTA (PCB).

patient	plain optimal balloon angioplasty (POBA)				paclitaxel-coated balloon (PCB)			
	MLD at last assessment or after reintervention (mm)	MLD at following assessments (mm)	LLL (mm)	LLL (% of original MLD)	MLD after PCB PTA or assessment after PCB PTA (mm)	MLD at following assessment (mm)	LLL (mm)	LLL (%)
1	7.6 ± 1.9	5.7 ± 1.0	2.1 ± 1.9	24 ± 22	6.3 ± 1.0	5.6 ± 0.5	0.6 ± 0.8	9 ± 13
2	7.9 ± 1.1	6.0 ± 0.8	1.9 ± 1.4	23 ± 15	7.1 ± 0.3	7.6 ± 0.7	-0.5 ± 0.6	-7 ± 8
3	7.7 ± 1.2	6.5 ± 0.9	1.2 ± 1.2	14 ± 16	7.5	5.6	1.9	25
4	8.5 ± 1.2	6.4 ± 2.3	2.1 ± 1.9	25 ± 21	6.2 ± 0.2	6.3 ± 0.3	-0.1 ± 0.5	-2 ± 8
5	8.5 ± 0.9	6.8 ± 1.5	1.8 ± 1.5	21 ± 18	7.6	6.9	0.7	9
6	8.6	3.1	5.5	64	7.8 ± 0.1	7.4 ± 0.6	0.4 ± 0.7	5 ± 9
mean ± SD	8.1 ± 0.5	5.8 ± 1.4	2.4 ± 1.5	28 ± 18	7.1 ± 0.7	6.6 ± 0.9	0.5 ± 0.8 ¹	7 ± 11 ¹

All values referring to individual patients are given as mean±SD of repeat observations in these patients before the use of a paclitaxel-coated balloon (first 4 columns) and after the use of a paclitaxel-coated balloon (last 4 columns). The line at the bottom of the table displays the mean±SD of the means of the 6 patients. PTA = percutaneous transluminal angioplasty; PCB = paclitaxel-coated balloon; LLL = late lumen loss; MLD = in-stent minimal lumen diameter.

¹ P < 0.05, uncoated balloon vs PCB.

patency in humans include intraluminal (in-stent) brachytherapy [22] and local delivery of motexafin gadolinium [23]. First studies in an animal model showed promising effects of local paclitaxel delivery on pseudointima hyperplasia [24]. Paclitaxel is a lipophilic chemotherapeutic taxane that causes irreversible stabilization of microtubules and thus interrupts the mitosis process. Its cytostatic effects have been shown in some tumor models [25]. Paclitaxel also inhibits the proliferation of smooth muscle cells [26, 27], which is one cause of in-stent hyperplasia [14, 26]. Lipophilicity of paclitaxel facilitates cell penetration and long residence time, which may underlie its long-term local efficacy [15, 26, 28]. Paclitaxel-mediated intimal hyperplasia inhibition has been reported for human femoroarterial [9, 10] and coronal in-stent stenosis [7] as well as for arteriovenous grafts [8]. The results presented here indicate that local delivery of a single paclitaxel dose can reduce neointimal hyperplasia and thus the secondary patency after PTA. Therefore, paclitaxel-coated balloon PTA may be a novel strategy to improve the outcome after treatment of TIPS in-stent restenoses. We performed a follow-up according to our standardized hospital protocol and our results indicate a long-term effect persisting for at least 18 months after paclitaxel-coated balloon PTA in a setting with frequent restenoses. The positive effect after a single paclitaxel administration is in line with the results of previous studies, which have shown a long persistence of paclitaxel in arterial vessel walls [29]. We found relatively high residual amounts of paclitaxel on our balloons (28 ± 9% of dose) compared with the use of this type of coating in coronary vessels (about 10% of dose) [11], which might be surface dependent. This finding, combined with a negligible proportion on sheaths (0.2 ± 0.1%) in our study, still suggests successful local administration of paclitaxel. Paclitaxel concentrations in venous blood in the first 4 hours after PTA were below the detection limit of our method (< 5 ng/ml plasma), suggesting systemic venous blood concentrations below 5 ng/ml. Data from the use of paclitaxel in tumor treatment indicate that plasma concentrations greater than 80 ng/ml are required for systemic effects [30]. This finding is consistent with those of a previous study [31] using PCB in the arterial system.

Our analysis of paclitaxel-coated balloons in the treatment of TIPS restenosis has several limitations. These include the small number of patients, the lack of blinding of physicians, the participation of only a single hospital, and the lack of a control group due to compassionate use of treatment. Also, this study included

mostly patients with bare metal stents and a long follow-up period, which does not match the current day-to-day standard of patients with endoprosthesis. However, these findings may encourage prospective and randomized studies to investigate new options in the prophylaxis and treatment of shunt dysfunction in patients with cirrhotic liver disease.

In conclusion, in our patients with recurrent in-stent stenoses in bare metal stents, a single PTA with paclitaxel-coated balloons (PCB) prolongs secondary patency without a systemic effect of paclitaxel.

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