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Treatment with a combination of bosentan and sildenafil allows for successful liver transplantation in a patient with portopulmonary hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) that occurs in the setting of cirrhosis and portal hypertension is referred to as portopulmonary hypertension (PPHTN). Liver transplantation (LTx) is curative, but the presence of moderate-to-severe PPHTN may be a contraindication for transplantation because of the elevated risk of peri- and post-transplantation morbidity and mortality. We report a successful liver transplantation in a patient with liver cirrhosis after treatment of moderate-to-severe PPHTN with a combination of the dual endothelin receptor antagonist bosentan and the specific phosphodiesterase-5 inhibitor sildenafil.

Keywords: Portopulmonary hypertension, cirrhosis, liver transplantation, bosentan, sildenafil

INTRODUCTION

Portopulmonary hypertension (PPHTN) is defined as a condition when the mean pulmonary arterial pressure (PAP) is higher than 25 mmHg at rest, the pulmonary vascular resistance is more than 120 dyn·s·cm^{-5}, and the pulmonary capillary wedge pressure is lower than 15 mmHg in the presence of portal hypertension (1). The frequency of PPHTN was found to be 2%-5% in hemodynamic studies (2). While the frequency is 3%-6% among patients who are awaiting liver transplantation, it rises to 16% in patients with refractory ascites (3). Annual mortality ranges from 24% to 60% if it is left untreated (3, 4). Currently, PPHTN is a rare but serious problem for transplant candidates. The operative risk is low in patients with mild PPHTN (PAP<35 mmHg). While mortality due to the transplant surgery itself is 50%-80% in patients with moderate PPHTN (PAP 35-45 mmHg), serious pulmonary hypertension (PAP>50 mmHg) often has a fatal course; thus, the transplant operation is contraindicated (3, 4).

No long-term randomized controlled trials have been conducted with respect to the treatment of PPHTN, and treatment guides have not been established; however, some case studies have been performed. Treatment is empirical, and some models influenced by the treatment of idiopathic pulmonary arterial hypertension (IPAH) were developed. Herein, we present a case of successful liver transplantation of a patient with liver cirrhosis after combination treatment with the dual endothelin receptor antagonist bosentan and the specific phosphodiesterase-5 inhibitor sildenafil.

CASE PRESENTATION

A 43-year-old male patient had been diagnosed with liver cirrhosis secondary to hepatitis B infection when he was 12 years old after he experienced bleeding from esophageal varices. He underwent a distal splenorenal shunt operation (Warren shunt) in 1982. He was followed without any problems for 20 years. In 2011, ascites developed due to liver cirrhosis and hepatic encephalopathy. Since the frequency of his hospitalizations due to hepatic encephalopathy increased, he was recommended for liver transplantation. His treatment regimen was propranolol 3x40 mg, ursodeoxycholic acid 3x250 mg, lactulose 1x10 g, pantoprazole 1x40 mg, insulin glargine 1x22 IU, furosemide 2x40 mg, and spironolactone 1x100 mg.

On physical examination, his arterial tension was 100/60 mmHg, and he presented with what was defined as "++ pretibial edema", diffuse ascites in the abdomen,

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Case Report

Table 1. Longitudinal functional capacity, hemodynamics and echocardiographic and laboratory findings

	Time course (months)					
	Baseline	Bosentan and sildenafil therapy		Liver transplantation		
Parameters	**0**	**3**	**6**	**0**	**6**	**12**
Functional capacity						
6-min walk distance (m)	210	250	330	340	500	600
NYHA Functional Class	III	II	II	II	I	I
Right heart catheter						
Mean PAP (mmHg)	45	-	33	-	-	-
PCWP (mmHg)	10		10			
Transpulmonary gradient (mmHg)	35	-	23	-	-	-
Pulmonary vascular resistance (dyn·s·cm^{-5})	422	-	310	-	-	-
Echocardiogram						
Systolic PAP (mmHg)	65	55	50	48	40	35
Right ventricular dilatation	Moderate	Moderate	Moderate	Moderate	Mild	Normal
Laboratory results						
Hemoglobin (g/dL)	15.3	15	15.1	14.8	15.4	15.2
Hematocrit (%)	45.1	44	44.5	43.7	45.8	45.5
Platelets (K/µL)	84	82	85	80	210	250
AST (IU/L)	22	24	25	21	20	24
ALT (IU/L)	9	11	13	12	12	12
Total bilirubin (mg/dL)	2.21	2.31	2.42	2.52	1.4	1.3
INR	1.93	2.1	1.72	1.56	1.34	1.1

NYHA: New York Heart Association; -: investigation not performed; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio

and jugular venous distention. His general state was moderate, his skin color was darkened, he was lethargic, and he presented with a flapping tremor of the hands. Echocardiography revealed a normal diameter and function of the left ventricle, mild mitral insufficiency, moderate tricuspid insufficiency, left atrial dilatation, and widening of the right atrium and right ventricle. The maximum systolic PAP was calculated as 65 mmHg from the tricuspid insufficiency flow, and the diastolic PAP was calculated as 35 mmHg from the pulmonary insufficiency flow. The estimated mean PAP was 45 mmHg according to the echocardiographic images. Coronary angiography indicated that the coronary arteries were normal, and the mean PAP was measured as 45 mmHg by right heart catheterization. To decrease the pulmonary hypertension and perform the transplantation, an out-of-indication drug approval for bosentan and sildenafil treatment was obtained from the Ministry of Health, and the combination therapy was administered. The initial dose of bosentan was 2x62.5 mg, while that of sildenafil was 3x20 mg. The drug doses were increased gradually with cautious follow-up, and the maximum doses were reached at the end of the first month (bosentan 2x125 mg, sildenafil 3x60 mg). The maximum doses were well-tolerated by the patient. No elevation was observed in the levels of liver enzymes, bilirubin, and INR, and no decrease in the hemoglobin level was observed (Table 1). In the sixth month of treatment with bosentan and sildenafil, the systolic PAP decreased to 50 mmHg on echocardiography, and the mean PAP by right heart catheterization regressed to 33 mmHg. His 6-minute walk test increased to 330 meters at the end of 6 months from the initial distance of 210 meters which was achieved prior to treatment with bosentan and sildenafil. His functional capacity changed from class III to class II. A liver from a cadaver was transplanted into the patient in December 2012 while he continued with this treatment regimen. Upon the observation of a decrease in dilatation of the right heart chambers and a regression of the systolic PAP to 45mmHg in the third postoperative month, sildenafil and then bosentan treatment were gradually stopped. In the sixth postoperative month, the patient's general state was good, he had no ascites or edema upon physical examination, his effort capacity was determined to be class I, and his systolic PAP was 40 mmHg. He also walked 500 meters in the 6-minute walk test. In the twelfth postoperative month, his effort capacity was desig-

nated as class I, and his systolic PAP was 35 mmHg according to the echocardiographic findings. In addition, he walked 600 meters in the 6-minute walk test. The clinical and laboratory characteristics and echocardiographic findings before and after transplantation are presented in Table 1.

DISCUSSION

Portopulmonary hypertension is a rare clinical condition with a poor prognosis in patients with cirrhosis. Pulmonary arterial hypertension may return to normal levels, and the disease may be resolved with a liver transplant; however, the perioperative and postoperative mortality is high in cases of pulmonary hypertension. The risk of mortality is close to 0% if the mean PAP is lower than 35 mmHg (5). However, the risk of mortality rises to 50% if the mean PAP is between 35-45 mmHg, and it increases to nearly 100% when the mean PAP is greater than 45 mmHg (3, 6). If the preoperative pressure is reduced to levels below 35 mmHg, transplantation may be performed confidently.

No clinical guidelines currently exist for the treatment of these patients because of the rarity of this condition. Instead, there are case presentations and case series, as well as clinical approaches and experiences. Advanced treatment techniques are applied in the case of portopulmonary hypertension. Prostacyclin, phosphodiesterase type 5 inhibitors, and lastly, endothelin receptor antagonists have been proposed for use as vasodilator agents.

To reduce the increased pulmonary pressure, epoprostenol, a prostacyclin analog, has been administered intravenously for many years. This treatment leads to vasodilation, the anti-aggregation of platelets, and antiproliferative effects. However, in one study, the treatment was stopped in half of the patients because of the following adverse effects: chin pain, diarrhea, erythema, arthralgia, infections, sepsis due to a catheter, thrombus, pump dysfunction, hypersplenism, impairment of liver function, and rebound pulmonary hypertension (7). Due to its excessive adverse effects and the difficulty with intravenous administration, inhaled iloprost has been the preferred treatment (6). Inhaled iloprost provides an enhancement in functional capacity; however, this improvement is not maintained in some patients. Additionally, hemodynamic improvement is not observed in angiographic right heart catheterization after treatment with iloprost (6). Briefly, until now, it has not been demonstrated that prostacyclins are sufficiently effective as treatments for portopulmonary hypertension.

Phosphodiesterase inhibitors have been successfully applied for the reduction of pulmonary arterial hypertension (8). They are well-tolerated and have a relatively mild adverse effect profile. They lead to vasodilation through nitric oxide-mediated smooth muscle relaxation. Reichenberger reported an enhancement in clinical, functional, and hemodynamic parameters in patients with PPHTN after 3 months of treatment with sildenafil (9). However, some researchers have speculated that sildenafil increases the hepatic venous pressure gradient and may trigger bleeding from esophageal varices due to elevated portal pressure (10). In contrast, some publications have demonstrated that the hepatic venous pressure gradient does not change, while others have shown that it decreases (10).

Primary pulmonary hypertension has been managed more successfully since the introduction of endothelin receptor antagonists (8,11). These drugs target endothelin-1, a strong vasoconstrictor. The levels of endothelin-1 in patients with cirrhosis and portopulmonary hypertension are typically elevated. Due to the increased levels of endothelin-1 in patients with cirrhosis and portopulmonary hypertension, it is considered to be directly responsible for the etiology of portopulmonary hypertension (11). Thus, the endothelin receptor blockers bosentan and ambrisentan are frequently used in these patients. Bosentan is the more widely used and more frequently studied drug. It is a dual endothelin receptor blocker and was approved by the FDA for use in patients with idiopathic PAH and mixed connective tissue disorders related to PAH. Its treatment dose (2x125 mg) in patients with idiopathic PAH induces the elevation of hepatic enzymes in 10% of patients (6, 11). While its use was previously avoided, it has become a preferable treatment due to the positive clinical response it induces. Bosentan may be administered according to the doses that are convenient for each individual, but cautious monitoring of hepatic enzymes is recommended. In a study by Hoeper et al., in which 11 patients who were treated with bosentan in 2005 were evaluated, the regression of symptoms, an enhancement in exercise capacity and functional capacity, an increase in peak O_2 expiration, and a reduction in pulmonary vascular resistance were reported (11). The six-minute walk test capacity increased from 315 meters to 388 meters after 1 year of treatment with bosentan. While half of the patients could tolerate a maximum dose of 2x125 mg, the other half was only able to tolerate2x62.5 mg. The treatment with sildenafil and iloprost administered along with bosentan demonstrates asynergistic relationship, and the patients show a quick recovery (6).

In conclusion, the primary goal of treatment with vasodilators in patients with portopulmonary hypertension is the reduction of the perioperative risk and the mortality and morbidity due to right-sided heart failure. Patients with pulmonary hypertension should be given appropriate and adequate treatment with vasodilators and followed cautiously; moreover, they should not be removed from the transplant list. The keys to an increase in survival may be specific treatments of the appropriate patients, the timing of the transplantation that is adjusted according to the echocardiographic imaging performed every 3 months, continuation of treatment after transplantation, and meticulous postoperative follow-up. In prior studies, while vasodilator treatment was given to patients with cirrhosis and low-to-moderate portopulmonary hypertension, transplantation was not performed on patients with severe portopulmonary hypertension due to the increased risk of mortality. However,

currently, an enhancement in survival and a reduction in pulmonary hypertension have been achieved with the combined or the single application of bosentan/ambrisentan, sildenafil, and prostacyclin analogs.

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