

[ORIGINAL ARTICLE]

Cell-free and Concentrated Ascites Reinfusion Therapy for Refractory Ascites in Cirrhosis in Post-marketing Surveillance and the Role of Tolvaptan

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Abstract:

Objective Ascites becomes refractory to diuretics in cirrhotic patients, who then require repeated large-volume paracentesis or cell-free and concentrated ascites reinfusion therapy (CART). The objective of this study was to confirm the safety and efficacy of CART, evaluate the actual situations with respect to the prescription of diuretics and determine the role of diuretics after the introduction of CART.

Patients and Methods We recruited 34 cirrhotic patients who received CART with concomitant diuretics using furosemide (76.2%), spironolactone (48.5%), thiazide (4.0%) and tolvaptan (53.5%) from a post-marketing surveillance of CART.

Results CART improved the tested clinical indices, i.e., body weight, abdominal circumference, performance status, dietary intake, total protein and albumin. The intervals of CART sessions were significantly prolonged in patients who received tolvaptan (mean, 22.5 days) compared to those not receiving tolvaptan (mean, 10.8 days) ($p < 0.001$). The drop-out rate was significantly decreased in patients receiving tolvaptan compared to those not receiving tolvaptan when drop-out was defined as paracentesis ($p < 0.05$).

Conclusion We confirmed that CART is an effective treatment for refractory ascites occurring in cirrhotic patients. The administration of tolvaptan in combination with CART leads to a significantly reduced rate of ascites accumulation.

Key words: liver cirrhosis, refractory ascites, cell-free and concentrated ascites reinfusion therapy, tolvaptan

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Introduction

Ascites is the pathologic accumulation of fluid in the peritoneal cavity and is a cardinal sign of disease progression (1, 2). Although sodium restriction and diuretics remain the cornerstones of management for ascites, many patients require additional therapy when they become refractory to this treatment. Patients who repeatedly receive large-volume paracentesis, which involves frequent hospital visits, experience a poor quality of life (QOL) (3, 4). In order to manage refractory ascites, some cirrhotic patients have selected

transjugular intrahepatic portosystemic shunt or peritoneovenous shunt to improve their QOL (5, 6). Over the past several decades, new interventions and methodologies have been introduced, such as peritoneal-urinary drainage and cell-free and concentrated ascites reinfusion therapy (CART) (7, 8).

The reinfusion of concentrated ascites was developed as a secondary modality to large-volume paracentesis in Japan. CART has been proven to be as safe and effective a treatment as large-volume paracentesis with albumin infusion (8). One of the primary benefits of CART is the reduced use of albumin. At present, the CART procedure may

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be more expensive than albumin infusion, depending on the amount of protein re-infused. However, albumin transfusion may cause infection and entails problems associated with the overuse of blood derivatives. In addition, insurance does not fully cover the cost of albumin. The manufacturer conducted post-marketing surveillance for CART from 2014 to 2015 and reported on the clinical data obtained from 147 patients undergoing a total of 356 sessions (9). Among the patients in this study, cancer was the most common primary disease (85.9%), followed by cirrhosis (11.4%).

The effect of the V2 receptor antagonist tolvaptan has been explored in combination with low-dose diuretics (furosemide ≥ 40 mg/day and spironolactone ≥ 25 mg/day; or furosemide ≥ 20 mg/day and spironolactone ≥ 50 mg/day) in cirrhotic patients with ascites (10, 11). In Japan, tolvaptan was approved for administration to hepatic cirrhosis patients with fluid retention in 2013. Recently, the combination of CART with diuretics was thought to be a useful treatment in patients with refractory ascites, but it has not been validated. We therefore grappled with the research question, “Can diuretics, including tolvaptan, extend the intervals between CART sessions of ascites patients?”

In the present study, we selected cirrhotic patients with ascites from among post-marketing surveillance data. We then evaluated the prescription of diuretics after the introduction of CART and the intervals of CART sessions with respect to each diuretic administration. In addition, we re-evaluated the safety and efficacy of CART in cirrhotic patients with refractory ascites.

Materials and Methods

Study design and patients

The post-marketing surveillance by the manufacturer was conducted in accordance with the Good Post-marketing Surveillance Practice, an ordinance of the Ministry of Health, Labour and Welfare. This study conforms to the provisions of the Declaration of Helsinki.

Twenty-two centers in Japan offering CART sessions were selected. All of the patients who underwent CART at each participating center from January 2014 to January 2015 were registered consecutively (9). Thirty-four of the 147 patients presented with liver cirrhosis and were included in this study. Cirrhosis was diagnosed based on liver function test values, diagnostic imaging with ultrasonography and computed tomography (CT), and the evaluation of esophageal varices on upper endoscopy. The diagnosis of hepatocellular carcinoma (HCC) was established via dynamic radiological findings using CT, magnetic resonance imaging (MRI) or angiography and clinical data. The HCC stage was determined as previously reported in studies for staging of HCC conducted by the Liver Cancer Study Group of Japan (12).

Survey items

The characteristics of patients in this study included the age, sex, the presence/absence of complications [i.e., chronic renal failure (estimate glomerular filtration rate (eGFR) <30 mL/min/m²), overt hepatic encephalopathy (present or past), esophageal varices and HCC, a history of ascites therapy (i.e., large-volume paracentesis), concomitant use of anticancer drugs and diuretics and the number of CART sessions during the surveillance period.

The following patient characteristics were examined: body weight, abdominal circumference, Eastern Cooperative Oncology Group (ECOG) performance status (PS), dietary intake and blood test results (13). Blood tests included a complete blood count (white blood cells, red blood cells, hemoglobin, hematocrit [Hct], and platelets), serum levels of total protein, albumin, total bilirubin, urea nitrogen, eGFR and creatinine. All adverse events that had a possible association with CART procedures or concomitant drugs were documented by the physicians caring for the patients.

CART procedure

The standard CART procedure is comprised of three steps: i) drainage of the ascites into a designated bag by abdominal paracentesis; ii) removal of malignant cells and bacteria by filtration and removal of excess fluid and electrolytes by concentration; and iii) reinfusion of the filtered and concentrated ascites (14). The amount of ascites collected was dependent on the parameters set forth by the individual centers. We investigated the appearance of the original ascites and amount and composition of the original and processed ascites. The amounts of total protein and albumin in ascites were estimated by multiplying the volume of ascites by the total protein concentration and albumin concentration, respectively.

It was possible that the circulating blood volume might change due to an increase in colloidal osmotic pressure during the re-infusion process. Based on the assumption that the volume of the erythrocytes remained unaltered by the CART procedures, we corrected the clinical indices by the following equation, taking into account the change in the Hct value (9):

Adjusted post-CART value = $\frac{\text{Post-CART value} \times (\text{pre-CART Hct value})}{(\text{post-CART Hct value})}$.

Statistical analyses

All data were expressed as the mean \pm standard deviation (SD) or proportion (%). Continuous data were analyzed by Student's *t*-test or a one-way analysis of variance, while categorical data were analyzed by the χ^2 test or Fisher's exact test. A paired *t*-test was used for comparing values before and after CART in the same patient. Relationships between variables were determined using the Spearman's correlation coefficient. The cumulative drop-out rates were estimated with the Kaplan-Meier method and compared between groups by the log-rank test. A logistic regression

Table 1. Patient Characteristics before CART Procedures.

Items	n=34, total 101 sessions
Age, years	68.7±10.6 (54-93)
Male/Female	27/7
Complications	
HCC	17 (50.0%)
chronic renal failure	8 (23.5%)
hepatic encephalopathy	3 (8.8%)
esophageal varices	7 (20.6%)
Details of CART procedures the number of sessions	3.0±2.9 (1-13)
Body weight (kg)	66.1±14.0 (47-104)
Abdominal circumferences (cm)	99.0±8.8 (76-120)
Previous history of large volume paracentesis	13 (12.9%)
Concomitant drugs	
anticancer drugs	3 (3.0%)
furosemide	77 (76.2%)
spironolactone	49 (48.5%)
thiazide	4 (4.0%)
tolvaptan	54 (53.5%)
Serum biochemistry	
albumin (g/dL)	2.4±0.5 (1.4-3.5)
total bilirubin (mg/dL)	2.1±2.9 (0.3-22.1)
eGFR (mL/min/1.73 m ²)	51.9±21.7 (9.7-119.9)

CART: cell-free and concentrated ascites reinfusion therapy, HCC: hepatocellular carcinoma, eGFR: estimate glomerular filtration rate

analysis was used for the multivariate analysis. Missing data were excluded from all analyses. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using the JMP software program, ver. 12.0 (SAS Institute, Cary, USA).

Results

Patient characteristics

The characteristics of study patients are shown in Table 1. We recruited 34 cirrhotic patients (27 men and 7 women). Seventeen of the 34 patients had HCC in addition to cirrhosis. The etiology of ascites was categorized based on transudative serum-ascites albumin gradient values (15, 16). Complications were found in 35.3% of cases. The number of CART sessions per patient during the surveillance period was 3.0±2.9 in cirrhotic patients. Concomitant medications taken during CART were anticancer drugs (3 doses, 3%), furosemide (77 doses, 76.2%), spironolactone (49 doses, 48.5%), thiazide (4 doses, 4%) and tolvaptan (54 doses, 53.5%).

Efficacy of CART procedures

Albumin infusion between pre- and post-CART was done in 6 (for a total of 20 sessions) of the 34 patients (total 101 sessions). We analyzed the changes in the CART procedure due to albumin infusion (for a total 20 sessions) while excluding 6 patients.

The characteristics of the ascites before and after the

CART procedures are shown in Table 2. The volume of processed ascites was 413±160 g after CART, giving a concentration ratio of 11.4 in terms of volume. The levels of total protein and albumin were 10.0±4.1 g/dL and 4.6±2.2 g/dL, and the calculated amounts of total protein and albumin were 40.6±22.1 g and 18.4±9.7 g, respectively. The clinical changes observed after CART compared to the patient status before CART are also shown in Table 2. Significant positive effects were observed in the body weight, abdominal circumference, dietary intake, ECOG PS and total protein and albumin levels. The Hct value after CART was significantly lower than that before CART, suggesting an increase in the circulating plasma volume, which potentiated a dilution effect. There was a significant elevation in the albumin level after CART (pre-CART, 2.3±0.5 g/dL vs. post-CART, 2.4±0.5 g/dL, $p<0.01$; post-CART corrected Hct, 2.5±0.5 g/dL, $p<0.01$). The degree of elevation in albumin is generally small due to a dilution effect. However, the results, when corrected for the changes in Hct, revealed a clear increase in the albumin level after CART, suggesting that CART replenished these factors. We observed no significant difference in other blood values, including white blood cells, red blood cells, hemoglobin, platelets, total bilirubin, urea nitrogen and creatinine (data not shown).

Role of diuretics

No patients were transferred to another hospital or died during the surveillance period. We found that two patients (three sessions) received paracentesis from one CART session to the next. We compared the interval of CART ses-

Table 2. Changes of Clinical Indices between Pre- and Post-CART.

	Pre-CART	Post-CART	p value
Amount and composition of ascites	Original ascites	Processed ascites	
ascitic fluid (g)	4,727.4±2,206.7	412.9±160.0	<0.001
total protein concentration (g/dL)	1.2±0.7	10.0±4.1	<0.001
albumin concentration (g/dL)	0.6±0.4	4.6±2.2	<0.001
total protein amount (g)	50.8±26.7	40.6±22.1	<0.001
albumin amount (g)	23.5±12.3	18.4±9.7	<0.001
Patients characteristics			
body weight (kg)	75.0±15.7	70.3±15.0	<0.001
abdominal circumferences (cm)	101.9±9.7	94.9±9.3	<0.001
dietary intake (%)	54.4±28.1	63.2±28.9	<0.001
ECOG PS (%)	2.4±1.0	2.2±1.1	<0.01
Serum biochemistry corrected Hct changes			
total protein (g/dL)	6.3±0.9	6.8±1.0	<0.001
albumin (g/dL)	2.3±0.5	2.5±0.5	<0.001
Serum biochemistry			
total protein (g/dL)	6.3±0.9	6.5±0.9	<0.05
albumin (g/dL)	2.3±0.5	2.4±0.5	<0.01

CART: cell-free and concentrated ascites reinfusion therapy, ECOG PS: Eastern Cooperative Oncology Group performance status, Hct: hematocrit

Table 3. Patient Characteristics and before CART Procedures in Patients with and without Tolvaptan.

	without tolvaptan (39 sessions)	with tolvaptan (22 sessions)	p value
Age, years	68.4±10.5 (56-93)	63.2±5.8 (56-73)	0.310
Male/Female	8/2	5/1	1.000
Complications			
HCC	7 (70%)	0	0.011
(I/II/III/IV)	(0/0/1/6)		
chronic renal failure	1 (10%)	0 (0.0%)	1.000
hepatic encephalopathy	1 (10%)	1 (16.7%)	1.000
esophageal varices	0 (0%)	2 (33.3%)	0.126
Body weight (kg)	63.8±7.1 (53-77)	76.8±21.3 (50-101)	<0.01
Abdominal circumferences (cm)	98.8±7.5 (76-107)	103.3±10.9 (90-120)	0.179
Previous history of large volume paracentesis	3 (7.7%)	0 (0.0%)	0.547
Concomitant drugs			
anticancer drugs	1 (2.6%)	1 (4.5%)	1.000
furosemide	18 (46.2%)	22 (100%)	<0.001
spironolactone	9 (23.5%)	21 (95.5%)	<0.001
thiazide	0 (0%)	3 (13.6%)	0.043
Serum biochemistry			
albumin (g/dL)	2.0±0.4	2.7±0.4	<0.001
total bilirubin (mg/dL)	2.0±0.5	2.0±1.1	0.912
eGFR (mL/min/1.73 m ²)	56.1±23.8	55.8±13.4	0.958
Amount and composition of ascites			
ascitic fluid (g)	3,825.3±1,429.7	5,458.9±2,296.7	<0.01
processed ascites (g)	362.4±156.8	369.1±125.7	0.867
total protein amount (g)	54.2±25.1	48.1±22.8	0.435
albumin amount (g)	21.1±11.4	27.6±9.5	0.073

CART: cell-free and concentrated ascites reinfusion therapy, HCC: hepatocellular carcinoma, eGFR: estimate glomerular filtration rate

sions between patients with and without tolvaptan, excluding 3 paracentesis sessions (3 sessions) and 14 sessions using an albumin preparation.

The characteristics of the study patients with or without tolvaptan are shown in Table 3. The historical incidence rate of furosemide, spironolactone and thiazide use was signifi-

cantly higher in cirrhotic patients who received tolvaptan than in those not receiving tolvaptan. The patients with co-existing HCC were only seen in the non-tolvaptan group. In addition, the serum albumin levels were significantly lower in the non-tolvaptan group than in the tolvaptan group. The intervals of CART sessions were significantly longer in patients who received tolvaptan (mean, 22.5 days) than in those not receiving tolvaptan (mean, 10.8 days) ($p < 0.001$, Fig. 1).

The drop-out rate tended to be lower in the patients receiving tolvaptan than in those not receiving tolvaptan when drop-out was defined as receiving paracentesis or using albumin (Fig. 2A). The drop-out rate was significantly lower in patients receiving tolvaptan than in those not receiving tolvaptan when drop-out was defined as receiving paracentesis

($p < 0.05$, Fig. 2B). We also calculated the rate of ascites accumulation (volume of ascites collected divided by the CART interval). The accumulation rates of ascites were 492.3 mL and 536.9 mL with and without tolvaptan, respectively, showing no statistical significance.

With respect to differences between the two groups, such as in albumin levels, we further investigated whether or not the baseline albumin levels and changes in albumin were related to the intervals of CART sessions. There were no relationships between the albumin levels and intervals of CART sessions ($r = 0.269$, ns; albumin, 1.4-2.2 g/dL vs. ≥ 2.3 g/dL, $p = 0.715$) nor between the changes in albumin levels and intervals of CART sessions ($r = 0.199$, ns; changes in albumin, -0.5-0.1 g/dL vs. ≥ 0.2 g/dL, $p = 0.591$). In addition, we did not detect any association between coexisting HCC and the intervals of CART sessions ($p = 0.836$) in this study.

Although a logistic regression analysis was performed to investigate the association between intervals of CART sessions and albumin levels, changes in albumin levels, presence of tolvaptan prescription and presence of HCC, none of these factors were found to be associated with CART intervals. There was also no marked difference in the intervals of CART sessions with respect to other diuretics, such as furosemide, thiazide or spironolactone.

Next, we evaluated the clinical changes between pre- and post-CART in patients with cirrhosis with or without tolvaptan treatment. The body weight was significantly higher after CART in patients with tolvaptan treatment than in those without tolvaptan treatment, although there were no marked difference between these patient groups concerning other factors, such as changes in abdominal circumference, dietary intake and EOCG PS (Table 4).

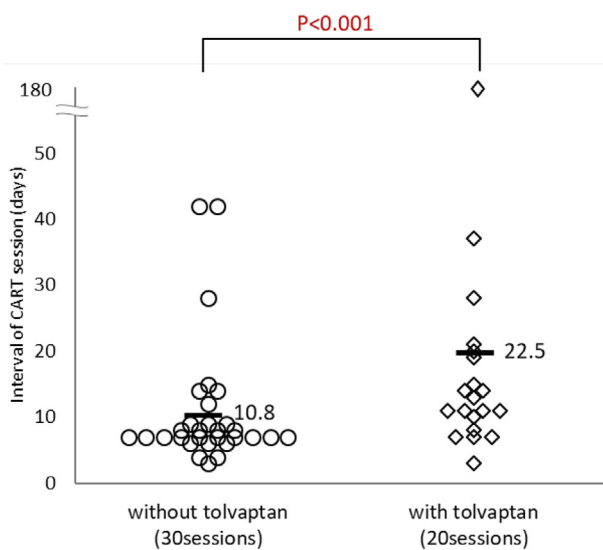


Figure 1. The intervals of CART sessions (days) in cirrhotic patients with or without tolvaptan, excluding patients who received paracentesis and albumin preparation. CART: cell-free and concentrated ascites reinfusion therapy

Frequencies of adverse events

Adverse events related to the drainage of ascites occurred in 4% of the recorded sessions (4/101). Adverse events included hypotension (3 cases), dyspnea (1 case) during/after

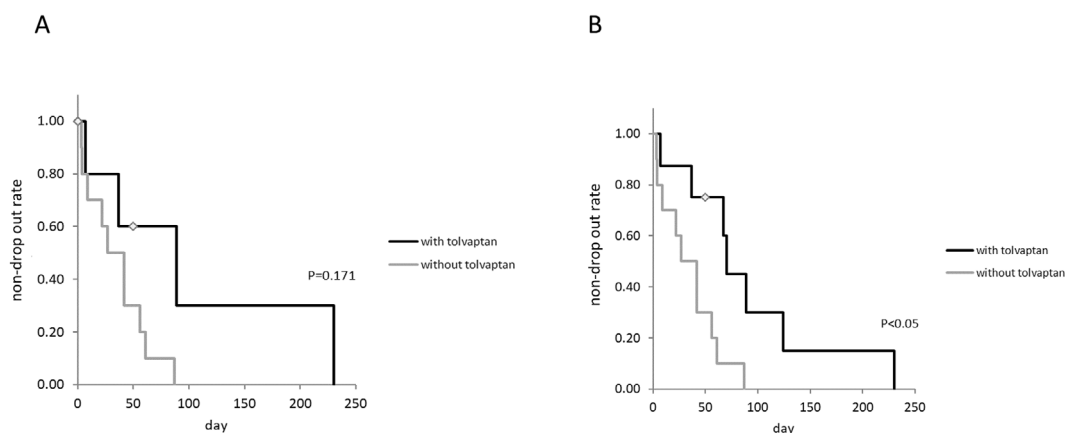


Figure 2. A: Drop-out tended to be lower in patients who received tolvaptan than in those not receiving tolvaptan when drop-out was defined as receiving paracentesis or using albumin. B: Drop-out was significantly lower in patients receiving tolvaptan than in those not receiving tolvaptan when drop-out was defined as receiving paracentesis.

Table 4. Changes of Clinical Indices between Pre- and Post-CART in Patients with or without Tolvaptan.

		without tolvaptan (39 sessions)	p value (pre vs. post)	with tolvaptan (22 sessions)	p value (pre vs. post)	p value (without vs. with tolvaptan)
Patients characteristics						
body weight (kg)	pre-CART	63.8±7.1		76.8±21.3		
	post-CART	60.5±7.3	<0.001	71.7±20.3	<0.001	
changes in body weight (kg)		-3.4±1.7		-5.1±1.7		<0.01
abdominal circumferences (cm)	pre-CART	98.8±7.5		103.3±10.9		
	post-CART	91.1±6.7	<0.001	94.4±12.1	<0.001	
changes in abdominal circumferences (cm)		-7.7±3.4		-8.9±4.0		0.373
changes in dietary intake (%)		6.6±12.4		6.3±25.3		0.967
changes in ECOG PS (%)		-0.2±0.4		-0.1±0.3		0.631
Serum biochemistry corrected Hct changes						
total protein (g/dL)	pre-CART	6.0±0.9		6.6±0.8		
	post-CART	6.6±1.2	<0.001	7.0±0.8	<0.05	
changes in total protein (g/dL)		0.7±0.7		0.3±0.5		0.105
albumin (g/dL)	pre-CART	2.0±0.4		2.7±0.4		
	post-CART	2.2±0.5	<0.01	2.9±0.4	<0.05	
changes in albumin (g/dL)		0.2±0.3		0.2±0.3		0.672
Serum biochemistry						
total protein (g/dL)	pre-CART	6.0±0.9		6.6±0.8		
	post-CART	6.3±1.1	<0.001	6.5±0.7	0.359	
changes in total protein (g/dL)		0.4±0.5		-0.1±0.6		<0.01
albumin (g/dL)	pre-CART	2.0±0.4		2.7±0.4		
	post-CART	2.2±0.5	<0.01	2.7±0.4	1.000	
changes in albumin (g/dL)		0.2±0.3		0.0±0.3		0.053

CART: cell-free and concentrated ascites reinfusion therapy, ECOG PS: Eastern Cooperative Oncology Group performance status, Hct: hematocrit

drainage of the ascites and hyperammonemia after reinfusion (1 case). Adverse events related to the reinfusion process occurred in 13.9% of sessions (14/101). The majority of adverse events were a fever and chills, and none were considered severe, with patients fully recovering from the events. Although the common adverse events related to tolvaptan treatment are thirst and pollakiuria, severe case of these symptoms were not reported. Neither increased bilirubin or sodium, acute renal failure nor hepatic encephalopathy were recorded.

Discussion

First, we reevaluated the safety and efficacy of CART in a post-marketing surveillance setting in patients with cirrhosis. CART improved tested clinical indices, i.e., body weight, abdominal circumference, dietary intake and ECOG PS, presumably due to the favorable protein replenishment effect. The study by the Kansai CART Study Group showed no marked changes in total serum albumin values (published in Japanese). However, the results, when corrected for the changes in Hct, revealed a clear increase in both total protein and albumin levels after CART, likely leading to a reduction in the required doses of albumin preparations to be administered. This study also showed an improvement in the PS. The alleviation of symptoms and the recovery of activities in daily life in cases of malignancy-related ascites were

reported after CART in a previous study, and this may be associated with an improvement in the PS (17). Generally, a fever is a significant problem in the clinical setting, but CART does not lead to a febrile state (18). Indeed, only mild and transient elevation of body temperature was observed in this study, which is in lockstep agreement with previous findings in patients with malignant ascites (9).

Both the European Association for the Study of the Liver and Japanese Society of Gastroenterology guidelines indicate that the first-line treatment for patients with refractory ascites is large-volume paracentesis coupled with the administration of intravenous albumin (2, 19). CART was developed in Japan as a surrogate for large-volume paracentesis (2). We confirmed in the present study that many patients received concomitant diuretics during CART, i.e., furosemide (76.2%), spironolactone (48.5%), thiazide (4.0%) and tolvaptan (53.5%). This study also revealed that most patients underwent multiple CART sessions. We found that cirrhotic patients administered tolvaptan had long intervals between CART sessions. The Japanese government approved tolvaptan for the treatment of hepatic edema in 2013. This diuretic is used in combination therapy to treat fluid retention in cirrhosis when existing diuretics, such as spironolactone and furosemide, fail to achieve a sufficient therapeutic effect (10, 11). Based on the results of this study, the combination of tolvaptan with CART may be useful for reducing the frequency of CART in patients with refractory ascites.

Therapeutic large-volume paracentesis or CART instantaneously relieves symptoms; however, despite experienced personnel on staff carrying out large-volume paracentesis followed by colloid volume expansion, circulatory dysfunction can still be induced (20, 21). This circulatory dysfunction may also facilitate the development of complications associated with paracentesis, such as hepatorenal syndrome, hyponatremia, hepatic encephalopathy and bacterial peritonitis (1). Therefore, patients who develop refractory ascites should not be exposed to multiple bouts of therapeutic large-volume paracentesis.

The present study had several limitations. There were differences between patients with and without tolvaptan, such as in the pre-CART albumin levels, frequency of HCC, amount of collected ascites, change in body weight and concomitant drugs. In addition, the results included multiple data from the same patients. We lacked information on the initiation of diuretics, including tolvaptan. This was an observational study, so the causal relationship of each factor with the outcome cannot be inferred. Prospective interventional studies in a large sample size will be required in the future.

The administration of tolvaptan in combination with CART leads to a significant reduction in the accumulation rate of ascites. This approach can be considered for patients who are not eligible for liver transplantation and who cannot tolerate repeated CART.

Author's disclosure of potential Conflicts of Interest (COI).

Motoh Iwasa: Honoraria, Otsuka Pharmaceutical. Ayako Isoai: Employment, Asahi Kasei Medical. Ryosuke Kobayashi: Employment, Asahi Kasei Medical. Naoko Torii: Employment, Asahi Kasei Medical. Noriko Soneda: Employment, Asahi Kasei Medical.

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