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Safety and Effectiveness of Cell-Free Concentrated Ascites Reinfusion Therapy in Gastric Cancer Patients with Refractory Ascites

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Abstract

Patients of gastrointestinal carcinoma with the refractory ascites are often chemotherapy-resistant cancer patients, and these patients are good indication of the cell-free and concentrated ascites reinfusion therapy (CART). CART is expected to improve symptoms associated with refractory ascites of patients with gastrointestinal carcinoma.

The aim of this study is to evaluate the safety and efficacy of the CART system performed on the gastric cancer patients with massive refractory ascites. In this retrospective observational study, we evaluated 5 CART processes performed 3 patients with the gastric cancer. We evaluated the effectiveness and adverse events during CART procedures. The amounts of collected and concentrated ascites were 2410.0 ± 1762.6 ml (mean ± SD), and concentration ratio was 10.5 ± 4.3 times. The amount of collected protein in ascites was 3.4 ± 1.3 g/dl, and concentration ratio of protein was 4.2 ± 2.0 times. Serum protein level was no significant different between before and two weeks after CART. No patients received an albumin (25% albumin preparation Alb) transfusion within two weeks prior to the first CART. Thus, CART allowed for the reduction doses of Alb to be administered. CART has been reported to cause two adverse reactions as elevation of body temperature and decrease in blood pressure. In our study, decreased blood pressure was not observed in all patients, and body temperature significantly rose after CART, but there were no patients more than 37 degrees.

In patients with refractory ascites of the gastric cancer patients in whom complete cure cannot be expected, CART improves their QOL and, in terms of medical economy, allows for the reduction doses of Alb. CART can be effectively applied as a palliative procedure for refractory ascites of the gastric cancer patients.

Keywords: Cell-free concentrated ascites reinfusion therapy; Gastric cancer; Refractory ascites; Palliative procedure

Introduction

The cancer often shows various symptoms, and one of the representative symptoms is ascites, and ascites produces organ dysfunction such as a stomachache, abdominal distention dyspnea dysphagia and as a result as for ascites patients become anorexia.

Moreover, especially ascites markedly impairs patient quality of life (QOL) by causing abdominal distention. Thus, ascites leads to deteriorate patient's QOL [1].

Although originally, the cell-free and concentrated ascites reinfusion therapy (CART) was used for refractory ascites caused by the end stage of chronic liver diseases in the decompensated stage but comes to be used for the carcinomatous ascites in present.

The representative article as to the CART procedures was published in 1977 by Inoue et al. [2].

The conventional CART system was approved by the National Insurance Scheme in 1981 in Japan, and has been used as a treatment for refractory ascites. By the way, CART is an ascites processing system. With this system, ascites is collected from patients filtered concentrated and infused to patients. At any facility equipped with this system, CART can be easily performed for the treatment of refractory ascites.

CART comprises three processes, first step: paracentesis, second step: removal of cell components from ascites by filtration and concentrating ascetic fluid and last step: reinfusion of fluid obtained through this process [3].

This report describes "the effectiveness and adverse events of CART for gastric patients with refractory ascites" at our hospital.

Patients

We conducted this retrospective observational study to examine patients who were treated with CART at Mito Medical Center from January to March 2017.

We examined 5 CART processes performed 3 gastric cancer patients with refractory ascites. Of the patients three were male, with mean age of 70.3 years old. Background of patients is shown in Table 1.

Background of patients who were treated with CART					
Items	**Patient 1**	**Patient 2**	**Patient 3**		
Age (years)	65	77	69		
Gender	M	M	M		
pStage	IV	IV	IV		
Cytology	V	I	II		
Chemotherapy	weekly PTX	weekly PTX	SOX		
Symptoms	abdominal distention anorexia	dyspnea anorexia	abdominal distention anorexia		
After CART	improve	improve	improve		
Number of CART	1	1	3		
Ascites (ml)			1st	2nd	3rd
Original	1750	600	3600	1250	4850
Processed	200	90	350	100	650

CART: Cell-Free and Concentrated Ascites Reinfusion Therapy. pStage: pathological stage of gastric cancer. Cytology: cytology of ascites. PTX: paclitaxel. SOX: TS-1+oxaliplatin.

Table 1: Background of patients who were treated with CART.

Cart procedure

Biologically clean ascites were obtained by paracentesis under local anesthesia. Drainage was continued until flow stopped spontaneously or was interrupted at the physicians' discretion [4,5]. We confirmed that endotoxins were not detected in the collected ascites, as it is known that CART is unable to eliminate endotoxin with filtration [6]. Therefore contraindication to CART is detection of endotoxin in ascites such as spontaneous bacterial peritonitis case. Ascites was processed at the rate 50~100 mL/min with CART system (apparatus: ACH- Σ, Asahi Kasei Medical, Tokyo Japan). Concentration method was internal pressure type system. The collected ascites was filtered through the columns of the AHF-MO model (Asahi Kasei Medical Tokyo, Japan) and filtered ascites was then concentrated using the columns of the AHF-UP model (Asahi Kasei Medical, Tokyo, Japan). Ascites did not accept fibrin formation in all processes at our patients therefore we did not use heparins for CART. The whole amount of ascites was processed in all sessions without the filter membrane becoming clogged during the processing. We performed the entire protocol for this study according to the rule of the Ethical Review Board of Mito Medical Center Ibaraki Japan.

Data Collection

We collected data for patient age gender ascites volume, ascites cytology and number of procedures. We evaluated laboratory data (serum protein; Pro, albumin; Alb, sodium; Na, potassium; K, chloride; Cl, hemoglobin; Hb, hematocrit; Ht, platelet; Plt and creatinine; Cr) and calculated estimated glomerular filtration rate (eGFR) in prior to CART and two week later. We also collected volume, protein and albumin concentrations and cell counts in ascites of pre- and post-CART. We defined the fever 38 degrees or more as <fever> in this study. All data were collected from medical records to perform this retrospective study to clarify the safety and clinical problems associated with CART.

Statistical Analysis

Results are given as means ± standard deviation (SD). Paired t-test was used for comparison of pre- and post-CART. All analyses were performed as two-tailed; P-values of <0.05 were considered as statistically significant.

Results

The CART improved the abdominal distension and dyspnea caused by ascites and, as a result, improved appetite of the patient. The processing amount of ascites is presented in Table 2. The amount of ascites processed in a single session was 2410.0 ± 1762.6 ml (range 600-4850 ml), and concentrated ascites was 278.0 ± 232.7 ml (90-650 ml). The concentration ratio (original/processed volume) of ascites was 10.5 ± 4.3 times (6.7-17.1 times). The amount of collected protein in ascites per session was 3.4 ± 1.3 g/dl (2.6-5.8 g/dl), and concentrated protein was 13.6 ± 5.7 g/dl (4.2-18.5 g/dl). The concentration ratio (original/processed volume) of protein in ascites was 4.2 ± 2.0 times (1.6-6.9 times). While, the amount of collected albumin in ascites per session was 1.7 ± 0.3 g/dl (1.5-2.1 g/dl), and concentrated albumin was 7.5 ± 3.2 g/dl (2.7-11.3 g/dl). The concentration ratio (original/processed volume) of albumin in ascites was 4.6 ± 2.2 times (1.8-7.5 times). Results of laboratory data were shown in Table 3. TP, Alb, Na, K, and Cl levels of pre and post CART were no statistically significant difference. No significant change in either Cr level or eGFR was observed between pre and post CART. CART did not affect renal function. Moreover no clinical problem occurred and correction was needed. On the other hand, either Hb or Ht level were 9.9 ± 1.1 mg/dL and 30.2 ± 4.4% before CART respectively, and both decreased to 9.4 ± 1.1 mg/dL and 28.8 ± 4.5% after the last CART respectively, showing statistically significant differences (P=0.008 and 0.006). However, no clinical problem occurred and correction was needed. The decrease of Plt count was found during CART, whereas Plt count was no statistically significant difference between pre and post CART.

Details of CART procedure				
	Original ascites	**Processed ascites**	**Concentration ratio (times)**	**P-value**
Collected ascites volume (mL)	2410.0 ± 1762.6 (range 600-4850)	278.0 ± 232.7 (90-650)	10.5 ± 4.3 (6.7-17.1)	0.036
Amount of protein in ascites (g/dL)	3.4 ± 1.3 (2.6-5.8)	13.6 ± 5.7 l (4.2-18.5)	4.2 ± 2.0 (1.6-6.9)	0.013
Amount of albumin in ascites (g/dL)	1.7 ± 0.3 (1.5-2.1)	7.5 ± 3.2 (2.7-11.3)	4.6 ± 2.2 (1.8-7.5)	0.0001
Values are mean ± standard deviation (SD). P-value by paired t-test. P-value of <0.05 were considered statistically significant. CaRT: Cell-Free and Concentrated Ascites Reinfusion Therapy.				

Table 2: Details of CART procedure.

Comparison of CART pre and post ascites, blood and physiological examination (3 patients and 5 times CART)			
	Pre-CART	**Post-CART**	**P-value**
Ascites			
TP (g/dL)	3.4 ± 1.3	13.6 ± 5.7	0.013
Alb (g/dL)	1.7 ± 0.3	7.5 ± 3.2	0.0001
Cell count	2545.2 ± 4251.5	0	
Volume (ml)	2410.0 ± 1762.6	278.0 ± 232.7	0.036
Blood			
TP (g/dL)	6.2 ± 1.2	6.6 ± 1.9	NS
Alb (g/dL)	2.9 ± 0.5	2.9 ± 0.3	NS
Na (mEq/L)	139.8 ± 3.9	140.3 ± 1.7	NS
K (mEq/L)	4.0 ± 0.6	4.0 ± 0.8	NS
Cl (mEq/L)	104.2 ± 3.0	105.0 ± 3.6	NS
Cr (mg/dL)	1.0 ± 0.4	1.1 ± 0.3	NS
eGFR	61.7 ± 16.9	56.4 ± 15.4	NS
Hb (g/dl)	9.9 ± 1.1	9.4 ± 1.1	0.008
Ht (%)	30.2 ± 4.4	28.8 ± 4.5	0.006
Plt (10^4/μl)	24.6 ± 9.1	20.5 ± 9.0	NS
Physiology			
Body temperature (°C)	36.3 ± 0.3	36.6 ± 0.2	0.046
SBP (mmhg)	111.8 ± 11.4	120.0 ± 17.3	NS
DBP (mmHg)	70.8 ± 7.9	70.0 ± 13.7	NS
HR (beats/min)	80.4 ± 11.5	77.2 ± 12.2	NS
Values are mean ± standard deviation (SD). P-value by paired t-test. P-value of <0.05 were considered statistically significant. CART: Cell-Free and Concentrated Ascites therapy. TP: total protein, Alb: alubumin, Na: sodium, K: potassium, Cl: chloride, Cr: creatinie, eGFR: estimated glomerular filtration rate, Hb: hemoglobin Ht: hematocrit, Plt: platelet, SBP: systolic blood pressure, DBP: diastolic blood pressure and HR: heart rate.			

Table 3: Comparison of CART pre and post ascites, blood and physiological examination (3 patients and 5 times CART).

By the way, the rise in temperature was found after CART, but required all no treatment in the 36 degrees level. Also, the significant change of the blood pressure and heart rate were not found during CART.

Discussion

Results of our study show that CART is a relatively safe and effective method for the refractory ascites of gastric cancer patients. And according to our study, CART has the several advantages. First, the technique of CART is simple and convenient. Second, protein loss would be unlikely. Third, there is little influence on patient's circulatory system and renal function. Fourth, CART allowed for the reduction of the required doses of the albumin preparations to be administered. Last, there is little risk of infection including viral hepatitis in comparison with use of FFP [7].

On the other hand, previous reports have shown that the adverse effect of CART. In short, CART has been reported to cause two adverse reactions as elevation of body temperature and decrease in blood pressure. In our study, decreased blood pressure was not observed in all patients. The circulatory dynamics were stable without hypotension.

And there were not the patients with fever 37 degrees or more during CART. Regarding elevation in body temperature caused by CART, there were previous several reports. Borzio et al. reported that 12% of their patients as pyrexia by CART [8]. And Zaak et al. reported that 43% of the patients was observed pyrexia by CART [9]. According to KANSAI CART STUDY GROUP, it was a report that ascites processing rate was associated with elevation of body temperature [10]. According to this report, the correlation that approximately 1°C increased at processing rate of 3000 ml/hr=50 ml/min was obtained. Endotoxin was considered as a candidate of the causes of this fever, but, according to the report of the Okamoto et al. that measured endotoxin during CART, the endotoxin was not actually detected in ascites at which point in time of the whole CART either [11]. Therefore it is hard to consider endotoxin as a cause of the fever by the CART. In our hospital, the CART performed at processing rate of 3000~6000 ml/hr=50~100 ml/min, but no patient had fever. Also, as for the Kao et al., polymorphonuclear leukocyte or lymphocytes during ascites attached to a filter device, and when ascites was filtered, shear stress had blood cells, and the activation of blood cells occurred, and inflammatory cytokine such as IL-6 was released from activated blood cells to concentrated ascites. They assumed that it was a cause of the fever (34). Orimi et al. reported that IL-6 did not increase by physical stimulation in ascites that took out outside a body subsequently. Therefore inflammatory cytokine represented by IL-6 is less likely to be a cause of the fever by the CART as well as endotoxin [12]. Thus so far the cause of the fever in the CART is unclear. However, according to our study, we think that we do not need to make a clinical problem about the fever at the CART. As a result, there was not the major problem by the CART, we were able to continue cancer chemotherapy. In contrast, although the decrease of Hb and Ht were found during an observation period, we considered about this for bone marrow suppression caused by chemotherapy.

In our study, we did not use the albumin preparations for albumin supplement during CART. With the CART procedure the required doses of the albumin preparations to be administered could be reduced. To infuse one 25% albumin preparation and FFP the expense is approximately JPY 7000 (USD 60), and 17000 (USD 150) respectively. Cost of blood product was curtailed by CART.

Our study had a limitation. This study was a retrospective observational study performed at a single center with very small number of patients. To conduct one CART procedure, the estimated expense was JPY 90 500 (USD 820; JPY 62 400 for material costs and JPY 28 100 for technical costs). CART is an expensive and time-consuming method. Therefore, it is important to produce suitable CART method and determine appropriate patient's indication of CART [3,4].

In patients with refractory ascites of gastric cancer patients in whom complete cure cannot be expected, CART improves their QOL and in terms of medical economy allows for the reduction in the required doses of albumin preparations to be administered. CART can be effectively applied as a palliative procedure for refractory ascites.

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References

1. Gotlieb WH, Feldman B, Moran FO, Zmira N, Kreizer D, et al. (1998) Intraperitoneal pressures and clinical parameters of total paracentesis for palliation of symptomatic ascites in ovarian cancer. Gynecol Oncol 71: 381-385.
2. Inoue N, Yamazaki Z, Oda T, Sigiura M, Wada T, et al. (1977) Treatment of intractable ascites by continuous reinfusion of the sterilized, cell-free and concentrated ascetic fluid. Trans Am Soc Artif Intern Organs 23: 699-702.
3. Ito T, Hanafusa N, Fukui M, Yamamoto H, Watanabe Y, et al. (2014) Single center experience of cell-free and concentrated ascites reinfusion therapy in malignancy related ascites. Ther Apher and Dial 18: 87-92.
4. Maeda S, Yabuuchi J, Nobuta H, Makiishi T, Hirose K (2015) Characteristics of patients and their ascites who underwent repeated cell-free and concentrated ascites reinfusion therapy. Ther Apher and Dial 19: 342-348.
5. Maeda O, Ando T, Ishiguro K, Watanabe O, Miyahara R, et al. (2014) Safety of repeated cell-free and concentrated ascites reinfusion therapy for malignant ascites from gastrointestinal cancer. Mol and Clin Oncol 2: 1103-1106.
6. Maeda A, Takeda K, Tsuruya K, Miura S, Toyonaga J, et al. (2012) A case of cell-free and concentrated ascites reinfusion therapy effective for ascites in spontaneous bacterial peritonitis in a renal transplant patient. Case Rep Nephrol Urol 2: 138-144.
7. Katou S, Tatsukawa H, Kondoh M, Inoue M, Ida K, et al. (1991) Prevention of the febrile reaction occurring on reinfusion of cell-free concentrated autogenous ascites. Jpn J Med 30: 311-317.
8. Borzio M, Romagnoni M, Sorgato G, Bruno S, Borzio F, et al. (1995) A simple method for ascites concentration and reinfusion. Dig Dis Sci 40: 1054-1059.
9. Zaak D, PaquetKJ, Kuhn R (2001) Prospective study comparing human albumin vs. reinfusion of ultrafiltrate-ascitic fluid after total paracentesis in cirrhotic patients with tense ascites. Z Gastroenterol 39: 5-10.
10. Takamatsu S, Sakikubo E, Ohata H, Abe S, Tanaka T, et al. (2014) Cell-free and concentrated ascites reinfusion therapy for liver cirrhosis. Japanese J Apher 33: 156-161 .
11. Okamoto Y, Nakahashi Y, Chino M, Matsuda K, Kubota T, et al. (2013) Towards the establishment of a safe cell-free and concentrated ascites reinfusion therapy. Jpn J Transfusion and Cell Ther 59: 470-475.
12. Orimi S, Mizuno K, Narahara M, Umakoshi H, Kaihara M, et al. (2011) A study of appropriate flow rate settings for cell-free and concentrated ascites reinfusion therapy and change of cytokine concentrations in ascites. Ther Apher Dial 15: 411-414.