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Research Article

Efficacy of Cell-Free and Concentrated Ascites Reinfusion Therapy for Malignant Ascites

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Keywords

- Malignant ascites
- Cancerous peritonitis
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Abstract

Cell-free and concentrated Ascites Reinfusion Therapy (CART) is a treatment method in which ascites retained by decompensated cirrhosis or cancerous peritonitis are drained from the body. Then, separation cleaning is performed by filtering the bacteria and tumor cells, and the autologous proteinsare concentrated and collected so that they can be reused. Although CART is expected to improve patients' symptoms and Quality of Life (QOL), there have beena limited number of studies showing the efficacy of CART in patients with Malignant Ascites (MA).In the present study, we investigated the safety and efficacy of CART performed for 13 patients with MA and compared the results with the efficacy of paracentesis performed for 10 patients with MA between January 2009 and January 2013. In total, 42 CART procedures were performed. The numbers of CART and paracentesis procedures performed per person were 3.4±2.6 and 3.8±1.2, respectively. CART appeared to control symptoms associated with retention of ascites, including abdominal fullness and anorexia, and the period of inability of oral intake before death was significantly shorter in the CART-treated patients (7.1±4.4 days) than in the paracentesis-treated patients (20.3±7.3 days; p=0.002). Moreover, the serum albumin levels were maintained in those patients without albumin infusion, and no clinically significant adverse effects, including fever during reinfusion, were not experienced. In conclusion, our results suggested that CART could be performed safely and could improve symptoms associated with ascites refractory to conventional treatment such as diuretics and salt restriction and, improve QOL in patients with MA.

ABBREVIATIONS

CART: Cell-free and Concentrated Ascites Reinfusion Therapy; Alb: Albumin

INTRODUCTION

Malignant Ascites (MA) is defined as abnormal accumulation of fluid in the peritoneal cavity as a consequence of cancer, and it presents a difficult clinical problem, causing discomfort and distress for many patients in the advanced stages of their disease [1]. The cancers most commonly associated with ascites are ovarian (37%), pancreato-biliary (21%), gastric (18%), esophageal (4%), colorectal (4%), and breast (3%) cancers [2]; up to 15% of all patients with gastrointestinal cancers developed ascites at some stage of their disease [3]. However, in up to 20% of all patients with MA, the primary tumor site remained undiagnosed [4]. MA accounts for a variety of symptoms, resulting in significant reductionsin patients' Quality of Life (QOL), including respiratory distress and dyspnea, abdominal tenderness and pain, nausea and anorexia, fatigue and impaired movement [5]. Moreover, abdominal fluid accumulation, principally in advanced oncological patients, promotes the development of abdominal infections and sepsis [4]. Although paracentesis, diuretics, and peritoneovenous shunting are the most commonly used procedures, there are no generally accepted evidence-based guidelines for the management of MA, in contrast to the treatment of underlying cancer [1]. Various medical and surgical palliative treatments have been proposed, but none of them has yet become established [5].

Cell-free and concentrated Ascites Reinfusion Therapy (CART) is a treatment method in which ascites retained by decompensated cirrhosis or cancerous peritonitis are drained from the body. Then, separation cleaning is performed by

filtering the bacteria and tumor cells, and the autologous proteins are concentrated and collected so that they can be reused [6]. Although previous reports have shown that decreased blood pressure and elevated body temperature are the two main presumed adverse events, CART is expected to improve patients' symptoms, reduce the risk of infection, and obviate the use of potentially expensive donated blood products [6]. However, there have been only a few recent studies showing the efficacy of CART in patients with MA. In the present study, we investigated the safety and efficacy of CART performed for patients with MA, compared with the efficacy of paracentesis.

MATERIALS AND METHODS

This retrospective study was conducted in accordance with the Declaration of Helsinki. Written informed consent under Institutional Review Board-approved protocols at Niigata University Graduate School of Medical and Dental Sciences (approval no. 282) was obtained from the enrolled patients.

Study cohort

Between January 2009 and January 2013, 23 patients with MA who were unresponsive to treatment, such as diuretics, were admitted to Tsubame Rosai Hospital, in Tsubame, Japan. Of these patients, 13patients who were treated with CART and 10 patients who underwent abdominal paracentesis were enrolled in the present study.

Procedures

Biologically clean ascites were obtained by paracentesis under local anesthesia. As much of the ascites fluid as possible was collected in a collection bag by gravity flow at a rate of 1.5-2.0l/h. At least 1l ascites were necessary to conduct CART proceeding. Ascites were processed at the rate of 50-60ml/min with the CART system (first filter AHF-MOW, second filter AHF-UP; Asahi Kasei Medical Co., Ltd., Tokyo, Japan).The ascites were filtered using the first filter, which removed cancer cells and microbes. Then, the filtered ascites were concentrated using the second filter by gravity or by clamping the filter outflow. In our preliminary experience, several cases showed slightly elevated body temperature, which could have been an adverse effect of CART. Therefore, 100 mg of hydrocortisone was administered to the patients before reinfusion. The concentrated fluid was drip-infused back into the patients at the rate of 100-150ml/h.

Statistical analysis

The significance of differences was statistically analyzed by Fischer's exact test, and variables were compared with the t test with Welch's correction, or the Mann-Whitney U test, using SPSS software (ver.18, SPSS Inc., Chicago, IL, USA). The level of significance was set at $p<0.05$.

RESULTS

Clinical features of the patients

Of the 13 patients with MA who underwent CART, 9were male, and 4 were female. The mean age of these patients was 70.4±6.9 years old (range: 54-84). The diagnosis of the patients included gastric cancer in 4 (30.8%), pancreatic cancer in 6 (46.1%), colon cancer in 2 (15.4%), and adrenal metastasis of lung cancer in 1 (7.7%). Of the 10 patients with MA who underwent paracentesis with albumin infusion, 5 were male, and 5 were female. The mean age of these patients was 76.7±9.0 years old (range: 60-88).The etiologies of the patients who underwent paracentesis included gastric cancer in 5 (50%) and pancreatic cancer in 5 (50%). The numbers of CART and paracentesis procedures performed per person were 3.4±2.6 and 3.8±1.2, respectively (p=0.629). In total, 42 CART procedures were performed during the period. The mean volume of processed ascites was 3200±600ml, and the ascites were concentrated to 330±270ml usingthe CART procedure. The process was performed at the mean rate of 2703±1256ml/h. In contrast, the mean volume of ascites withdrawn by paracentesis was 1733±664ml at a time. Although the paracentesis was performed with concurrent albumin infusion, the withdrawn volume of ascites was limited, mainly due to hypotension. Information regarding the patient profiles and the results of CART and paracentesis is summarized in Table 1.

Outcomes of CART and paracentesis

The mean survival times from the diagnosis of cancer were 14.6±12.0 months in patients who underwent CART and 9.8±3.4 months in patients who underwent paracentesis (Table 2). After the cause of massive ascites was diagnosed as cancerous peritonitis, the intent of treatment for ascites was palliative, and improvement in QOL was a priority. Although MA were often highly resistant to diuretic use, diuretics and salt restriction were applied in the patients with MA as first-line treatment. After the ascites appeared to be refractory to the initial treatment, CART or paracentesis was applied in the patients. The period between the start of those procedures for ascites and death was 59.2±47.9 days in patients who underwent CART and 31.0±5.1 days in patients who underwent paracentesis. The patients who underwent CART could maintain oral intake until 7.1±4.4 days before death, while the patients who underwent paracentesis could maintain oral intake until 20.3±7.3 days before death. CART appeared to continue to suppress symptoms associated with retention of ascites, including abdominal fullness and anorexia, and the period of inability of oral intake before death was significantly shorter in the CART-treated patients than in

Table 1: Patient characteristics and results of procedures for malignant ascites.

	CART	Paracentesis	P-value
n	13	10	-
Gender (female / male)	4 / 9	5 / 5	0.417
Age (years) (range)	70.4 ± 6.9 (54-84)	76.7± 9.0 (60-88)	0.106
Etiologies (gastric ca. / pancreatic ca./ colon ca. / adrenal meta. of lung ca.)			
	4 / 6 / 2 / 1	5 / 5 / 0 / 0	0.617
Number of procedures per patient (times)			
	3.4± 2.6	3.8± 1.2	0.629
Drained ascites volume (ml)	3,200 ± 600	1733 ± 664	<0.001
Processing speed (ml/h)	2,703± 1,256	-	
Concentration rate (times)	10.2 ± 2.8	-	
Processed ascites volume(ml)	330± 270	-	

Abbreviations: CART: Cell-free and concentrated Ascites Reinfusion Therapy; ca: Cancer; meta: Metastasis.

Table 2: Outcomes of procedures for malignant ascites.

	CART	Paracentesis	P-value
n	13	10	-
Survival from the diagnosis of cancers (months)			
	14.8 ± 12.0	9.8 ± 3.4	0.175
Period betweenthe start of procedures for ascites and death (days)			
	59.2 ± 47.9	31.0 ± 15.1	0.241
Durationof inability of oral intake until death (days)			
	7.1 ± 4.4	20.3 ± 7.3	0.002
Duration of instillation therapyuntil death (days)			
	9.2 ± 3.4	20.9 ± 7.4	0.003
Serum Alblevel before the start of procedures for ascites (g/dl)			
	1.8 ± 0.4	2.2 ± 0.4	0.077
Total dose of Alb infusion per person (g)			
	3.8 ± 13.9	52.5 ± 52.5	0.018
Serum Alblevel immediately before death (g/dl)			
	1.8± 0.3	1.8± 0.5	0.955

Abbreviations: CART: Cell-free and concentrated Ascites Reinfusion Therapy; Alb: Albumin

the paracentesis-treated patients (p=0.002) (Table 2). Therefore, the period that instillation therapy was necessary because of inability of oral intake in the patients who underwent CART was 9.2±3.4 days before death, which was significantly shorter than that of the patients who underwent paracentesis (20.9±7.3 days before death; p=0.003). Moreover, in the CART-treated patients, serum albumin levels were maintained from 1.8±0.4g/dl at the start of CART to 1.8±0.3g/dl immediately before death after several CART procedures. In contrast, serum albumin levels in the paracentesis-treated patients decreased from 2.2±0.4g/dl at the start of paracentesis to 1.8±0.5g/dl immediately before death after several paracentesis procedures, while the total dose of infused albumin per person was 53.5±52.5g in these patients. We did not experience any significant elevation of body temperature using hydrocortisone during the infusion process (data not shown) or any clinically significant adverse effect in patients who were treated with CART.

DISCUSSION

In the presents study, we investigated the efficacy of CART, mainly on the clinical course of patients with MA, compared to the efficacy of paracentesis with albumin infusion. CART appeared to control symptoms associated with retention of ascites, including abdominal fullness and anorexia, and the period of inability of oral intake before death was significantly shorter in the CART-treated patients than the paracentesis-treated patients. Moreover, serum albumin levels were maintained in those patients without albumin infusion, and no clinically significant adverse effects, including fever during reinfusion and hypotension, were not experienced. Therefore, we concluded that CART could be performed safely and could improve symptoms associated with ascites and QOL in patients with MA.

The pathophysiology of MA is multifactorial and remains incompletely understood [1,5]. Ascites might result from obstruction of lymphatic drainage by tumor cells that prevent absorption of intraperitoneal fluid and protein. Because the ascites of many patients with MA have high protein content, alteration in vascular permeability has been implicated in the pathogenesis of ascites production [1,7]. Molecules such as Vascular Endothelial Growth Factor (VEGF), Vascular Permeability Factor (VPF), interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF) might play rolesin altering vascular permeability [8,9]. In addition, a hormonal mechanism is involved in MA because the increase in ascites causes a depletion in circulating blood volume, with consequent activation of the renin-angiotensin-aldosterone system and sodium retention [3,5]. Therefore, reduced sodium intake, together with diuretics, has been recommended as first-line treatment in selected patients, but there is no consensus on its effectiveness [1,2].

In contrast to diuretics, or in some patients resistant to diuretics, therapeutic paracentesis yields temporary relief in approximately 90% of patients [1,8]. Complications are infrequent and can include secondary peritonitis, perforation, hypoproteinemia, pulmonary embolism, and hypotension [8]. Although paracentesis is the most common and effective modality for relieving symptomatic ascites, recurrence is a common issue, and many patients require multiple paracentesis procedures [10]. In addition, peritoneovenous shunts, including the Le Veen shunt [11] and the Denver shunt [12], have become popular in procedures for managing MA. However, due to potential risks during the procedure and aftercare, peritoneovenous shunting should be used when other treatment option have failed and when the life expectancy of the patient is sufficiently long to derive a benefit [2].

CART is a treatment that maintains albumin and globulin by filtration, concentration, and reinfusion of drained ascites. During the process of CART, the membrane separation technique is used, which resembles apheresis therapy [13]. The first filter passes proteins and other molecules with fluid, but does not pass cells or micro-organisms. Then, the second filter is virtually equal to a dialysis filter, ultrafiltrating isotonic salt and water from the filtered ascites and concentrating the final product [13]. Because the first membrane becomes clogged after processing approximately 2l cancerous ascites that are rich in cellular and mucinous components, novel CRAT (KM-CART), which includes a membrane cleaning function, was also developed [14]. Orimiet al. reported that a low flow rate of 50ml/min was the most appropriate condition for filtration and concentration during CART in order to collect total protein and albumin [6]. In the present study, we set the flow rate at 50-60ml/min, and the drained ascites were concentrated at 10.2 ± 2.8 times. Representative results of albumin concentrations in ascites from the patients were 0.71g/dl before CART and 5.39g/dl after the concentration. Recently, Ito et al. reported their experiences with CART in 24 patients with MA. Consistent with the present study, the authors concluded that CART could be performed safely in patients with MA and that CART might improve diuresis [13]. Because bilirubin cannot be eliminated through the first filter, CART is not applicable for patients with severe jaundice or hemorrhagic ascites. However, CART appears to be effective for improving the QOL of patients with MA.

CONCLUSION

In the present study, we demonstrated the efficacy of CART,

mainly on the clinical course of patients with MA, compared with the efficacy of paracentesis with albumin infusion. Although we recognize that the present study had several limitations, including its retrospective, observational nature, its single-institution experience, and the limited number of enrolled patients, our results suggested that CART could be performed safely and could improve symptoms associated with ascites that are refractory to conventional treatment, such as diuretics and salt restriction, and improve QOL in patients with MA.

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