

A Case Enabled Continuous Chemotherapy and Improved Quality of Life by Frequently Performing of Cell-Free and Concentrated Ascites Reinfusion Therapy (CART) in Terminal Lung Cancer Patients

メタデータ	<p>言語: eng</p> <p>出版者:</p> <p>公開日: 2021-07-13</p> <p>キーワード (Ja):</p> <p>キーワード (En):</p> <p>作成者: 椿, 貴佳, 児玉, 麻衣子, 武藤, 悠平, 佐藤, 譲之, 安齋, 正樹, 小林, 美貴, 上谷, 幸男, 浦井, 真友美, 廣野, 靖夫, 五井, 孝憲, TSUBAKI, Takayoshi, KODAMA, Maiko, TAKETOU, Yuuhei, SATOU, Masayuki, ANZAI, Masaki, KOBAYASHI, Miki, KAMITANI, Yukio, URAI, Mayumi, HIRONO, Yasuo, GOI, Takanori</p> <p>メールアドレス:</p> <p>所属:</p>
URL	<p>http://hdl.handle.net/10098/00028735</p>

A Case Enabled Continuous Chemotherapy and Improved Quality of Life by Frequently Performing of Cell-Free and Concentrated Ascites Reinfusion Therapy (CART) in Terminal Lung Cancer Patients

TSUBAKI, Takayoshi¹⁾²⁾⁴⁾, KODAMA, Maiko¹⁾²⁾, TAKETO, Yuuhei²⁾, SATO, Masayuki³⁾,
ANZAI, Masaki³⁾, KOBAYASHI, Miki¹⁾²⁾, KAMITANI, Yukio²⁾, URAI, Mayumi¹⁾²⁾,
HIRONO, Yasuo¹⁾²⁾⁴⁾ and GOI, Takanori⁴⁾

*Cancer Promotion Care Center, University of Fukui Hospital*¹⁾

*Palliative Care Team, University of Fukui Hospital*²⁾

*Respiratory Medicine, Division of Medicine, Faculty of Medical Sciences, University of Fukui*³⁾

*First Department of Surgery, Division of Medicine, Faculty of Medical Sciences, University of Fukui*⁴⁾

肺がん終末期での腹水濾過濃縮再静注法の頻回施行により QOL の改善が認められた 1 例

椿 貴佳¹⁾²⁾⁴⁾, 児玉 麻衣子¹⁾²⁾, 武藤 悠平²⁾, 佐藤 譲之³⁾, 安齋 正樹³⁾,
小林 美貴¹⁾²⁾, 上谷 幸男²⁾, 浦井 真友美¹⁾²⁾, 廣野 靖夫¹⁾²⁾⁴⁾, 五井 孝憲⁴⁾

医学部附属病院 がん診療推進センター¹⁾, 同緩和ケアチーム²⁾, 同呼吸器内科³⁾, 同第一外科⁴⁾

Abstract:

Background: Ascites fluid accumulation due to carcinomatous peritonitis causes symptoms such as nausea, anorexia, and abdominal distention. It significantly reduces the patient's Quality of Life (QOL) and makes it difficult to continue treatment. Cell-free and concentrated ascites reinfusion therapy (CART) is a treatment for a patient with cancerous refractory ascites, which ascitic fluid is withdrawn from the patient into the bag, then ascitic fluid is filtrated to remove bacteria and cancer cells, and furthermore ascitic fluid including helpful materials such as albumin is administered to the patient by the parenteral rout after concentrating. It is possible to relieve symptoms caused by refractory ascites. We report a case of a patient with terminal lung cancer who was able to continue chemotherapy and improve QOL by frequent CART.

Case presentation: A 45-year-old man came to University of Fukui Hospital with a chief complaint of severe pain in the upper abdomen. A computed tomography (CT) scan revealed a right upper lobe lung cancer, liver metastases and multiple lymph nodes metastases. Therefore, chemotherapy was initiated. Chemotherapy with cisplatin, pemetrexed sodium hydrate, and bevacizumab was administered up to the seventh-line treatment, but the results were all progressive disease. At that time, liver metastasis and para-aortic lymph node metastasis increased, resulting in worsening of ascites and abdominal distension, and CART was introduced. By continuing 14 cycles of CART, the patient's general condition could be maintained, and chemotherapy could be continued up to the tenth line. His activities of daily living were improved and he was able to continue his own work and enjoy his personal time.

Conclusion: We experienced a case in which frequent CART was performed to continue chemotherapy and to improve QOL in terminal lung cancer patients. CART is effective in maintaining the general condition and QOL of patients with refractory ascites, as well as opioid use and psychosocial care. The introduction of CART into patients with refractory ascites should be proactively considered.

Keywords: Cell-free and concentrated ascites reinfusion therapy (CART), refractory ascites, palliative care, Activities of Daily Living (ADL), Quality of Life (QOL)

要旨

上腹部の激痛を主訴として福井大学病院を来院した45歳男性において、画像検査により右上葉肺がんを原発とする肝転移および多発リンパ節転移を認められたので、シスプラチン、ペメトレキセドナトリウム水和物、およびベバシズマブを用いた化学療法が開始された。7次治療まで施行したが、依然として進行性の病態にあり、肝転移巣の増大による腹水の増悪が認められた。がん性腹膜炎による腹水貯留は、嘔気、食欲不振、腹部膨満感といった症状の原因となり、患者のQOLを低下させ、治療継続を困難とするので、腹水濾過濃縮再静注法 (Cell-free concentrated ascites re-infusion therapy, CART) を施行した。14回のCART施行により、全身状態は維持され、化学療法を10次治療まで継続することが可能であった。それにより、日常生活動作は改善し、仕事や私生活を充実させることが可能となった。CARTは難治性腹水を認めるがん終末期患者の全身状態、QOL維持、および緩和ケアとして有効であり、当該患者へのCART施行導入が積極的に検討されるべきと考ええる。

キーワード: CART, 難治性腹水, 緩和ケア, ADL, QOL

(Received 26 February, 2021 ; accepted 11 May, 2021)

Introduction

Typical symptoms of massive ascites include abdominal distention, dyspnea, and loss of appetite. Such symptoms may severely degrade the patient's quality of life¹⁾ and affect motivation for treatment. There are many causes of ascites, including cirrhosis, malignancy and infection²⁾. Ascites removal by paracentesis is effective in relieving symptoms such as abdominal distension and loss of appetite, but it also causes loss of protein in the ascites, which affects circulatory dynamics³⁾. Cell-free and concentrated ascites reinfusion therapy (CART) is a treatment method in which ascites fluid is collected, filtered to remove blood cells and other unnecessary components, and then concentrated with necessary components such as albumin and globulin, which are injected back into the body intravenously¹⁾. We report a case of a terminal lung cancer patient who was able to improve his Quality of Life (QOL) and continue treatment by frequent CART.

Case presentation

A 45-year-old man came to our hospital with a chief complaint of severe pain mainly in the right upper abdomen. He had been feeling discomfort in the same area for about two months, but he was too busy with work to go to the hospital. His medical history included duodenal ulcer and arrhythmia. He was in the construction business for many years, but he had no

history of asbestos exposure. His smoking history was 20 cigarettes per day for 30 years. There was no family history of cancer. No specific medications or allergies were noted. On physical examination, the patient had a height of 172.3 cm, a body weight of 63.9 kg, a pulse of 66 beats/minute, a blood pressure of 160/93 mmHg, and a body temperature of 37.0 °C . Anemia, jaundice, edema and malnutrition were not found. Cervical lymph nodes and thyroid gland were not palpated. Respiratory sounds were clear and there was no difference between left and right lung. His abdomen was flat and soft, and there was no spontaneous pain or tenderness, but the liver was palpated below the right costal arch about two transverse fingers. Laboratory tests on admission day showed that lactate dehydrogenase level of 1297 U/L and carcinoembryonic antigen level of 13400.3 ng/mL (Table 1). Chest X-ray showed a mass in the right upper lung field, and thoracoabdominal contrast-enhanced computed tomography (CT) showed a large mass of 19 mm in the right upper lobe (Fig 1 A), left superior mediastinal and left supraclavicular fossa lymph node metastasis (Fig 1 B), multiple liver metastases (Fig 1 C), and para-aortic lymph node metastasis (Fig 1 D). The diagnosis of right lung cancer (adenocarcinoma) was made by bronchoscopic biopsy. It was staged as cT1aN3M1b Stage IV (according to seventh edition of UICC classification), and chemotherapy with cisplatin, pemetrexed sodium hydrate, and bevacizumab was

Table 1. The laboratory data on admission

White blood cell count	11200 / μ L	AST	41 U/L
Hemoglobin	14.8 g/dL	ALT	44 U/L
Platelet	271×10^3 / μ L	ALP	451 U/L
CRP	0.45 mg/dL	γ -GTP	262 U/L
Total protein	7.5 g/dL	T-bil	0.8 mg/dL
Albumin	4.4 g/dL		
BUN	15 mg/dL	CEA	13400.3 ng/mL
Creatinine	0.91 mg/dL	SCC	0.4 ng/mL
LD	1297 U/L	SYFRA21-1	9.7 ng/mL

CRP: C-creative protein, BUN: blood urea nitrogen, LD: lactate-dehydrogenase
 AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkali phosphatase
 γ -GTP: γ -glutamyltransferase, T-bil: total bilirubin, CEA: carcinoembryonic antigen
 SCC: squamous cell carcinoma associated antigen, SYFRA: cytokeratin subunit 19 fragment

started in the same month. Both the patient and his wife were upset at the time of notification, but as time passed, they regained their composure and were able to start treatment. Their child was independent and understood the disease. He was positive about the treatment, asking questions to his doctor about the treatment plan.

By four years and six months after the first chemotherapy, up to the seventh-line treatment was given, but the treatment effect was poor, and the results were all progressive disease. The liver metastases once shrank but recurred in S7 and tended to increase (Fig 2 A) and metastases in the abdominal lymph nodes was also increased (Fig 2 B). Ascites fluid accumulation was evident (Fig 2 C). The patient complained of abdominal distension, so paracentesis was performed. 3100 ml of ascites was drained, and the patient's weight decreased from 61 kg to 58 kg. The ascites was yellow and slightly cloudy, and cytology showed atypical cells with a high N/C ratio (class V). Based on imaging and clinical findings, cirrhosis and infection were unlikely.

It was considered consistent with malignant ascites caused by liver metastasis and intra-abdominal lymph node metastases of primary lung cancer. Just one week later, his weight had returned to 61.5 kg and abdominal circumference had increased to 90 cm. Diuretics were also administered (spironolactone 25 mg/day), but the rate of accumulation was rapid and frequent paracentesis was expected to be necessary. However, the patient's general condition needed to be maintained for the continuation of chemotherapy in the future, so we decided to introduce CART. He agreed to CART because he wanted to do what he could and wanted to move as much as possible.

A total of 14 sessions were performed from the introduction to the last chemotherapy treatment day, with an average of 12.2 days (range 7-45 days) from the last session. The average volume of fluid drained per session was 4921 ml, and the average volume of re-infused fluid was 197 ml. The changes in body weight, abdominal circumference, body temperature and blood pressure

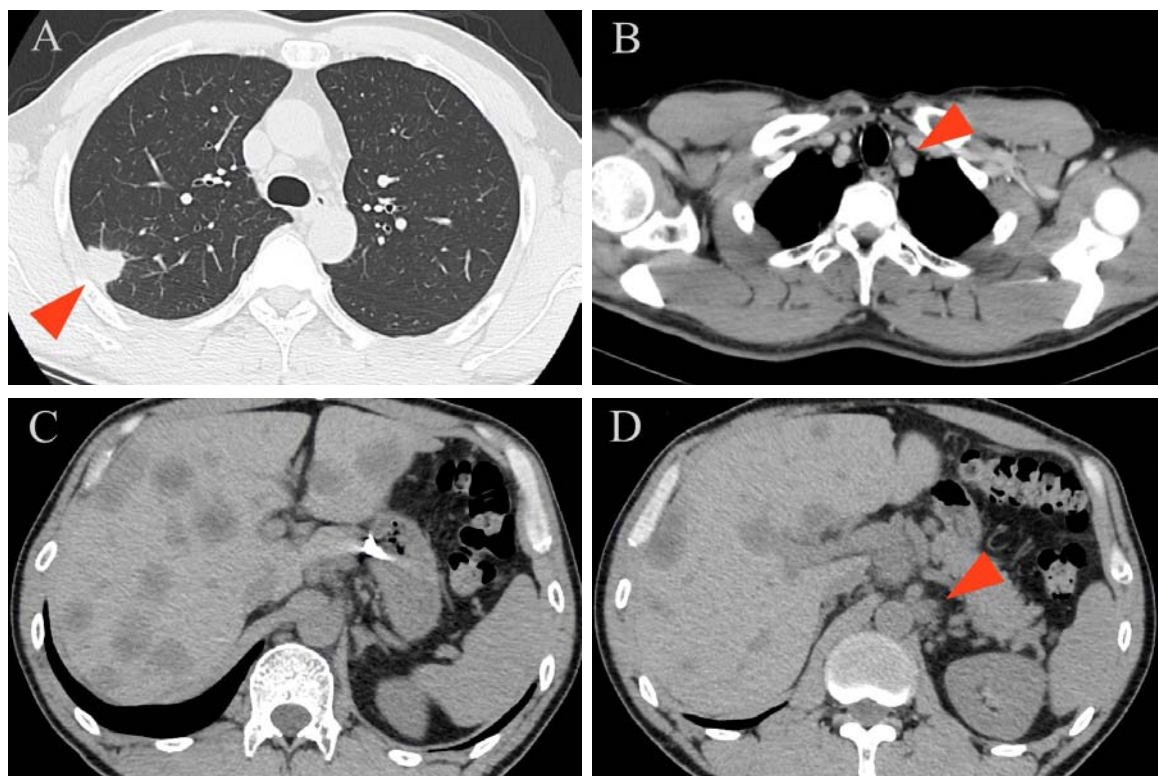


Figure 1. Chest and abdomen CT findings. A: Chest CT showed a 19 mm mass in the upper lobe of the right lung (arrowhead). B: Multiple liver metastases across both lobes. C: Para-aorta lymph node metastasis was positive (arrowhead). D: Contralateral mediastinal lymph node metastasis was also positive (arrowhead).

before and after intravenous infusion were analyzed using paired t-tests. The mean weight before and after CART was 56.8 kg and 51.7 kg respectively, which was a significant decrease ($P<0.05$). The mean abdominal circumference was also significantly reduced, from 91.9 cm before to 84.8 cm after the procedure ($P<0.01$). These were thought to be very effective in improving subjective symptoms, with comments such as no more feeling of fullness, increased frequency of urination, increased activity and relief of abdominal fullness. There was no significant difference in the mean change in body temperature and blood pressure during and after

the intravenous infusion compared to before it ($P<0.05$) (Table 2). As for the laboratory tests, compared to before the introduction of CART, hemoglobin levels were maintained for most of the time, and albumin, a measure of nutrition, was almost maintained (Fig 3). During this period, no concentrated red blood cell transfusions or albumin products were administered. Creatinine and transaminase levels did not change significantly, so renal and hepatic functions were thought to have been preserved (Fig 4). His general condition was considered to be maintained. As a result, chemotherapy could be continued, and we could administer the eighth to tenth

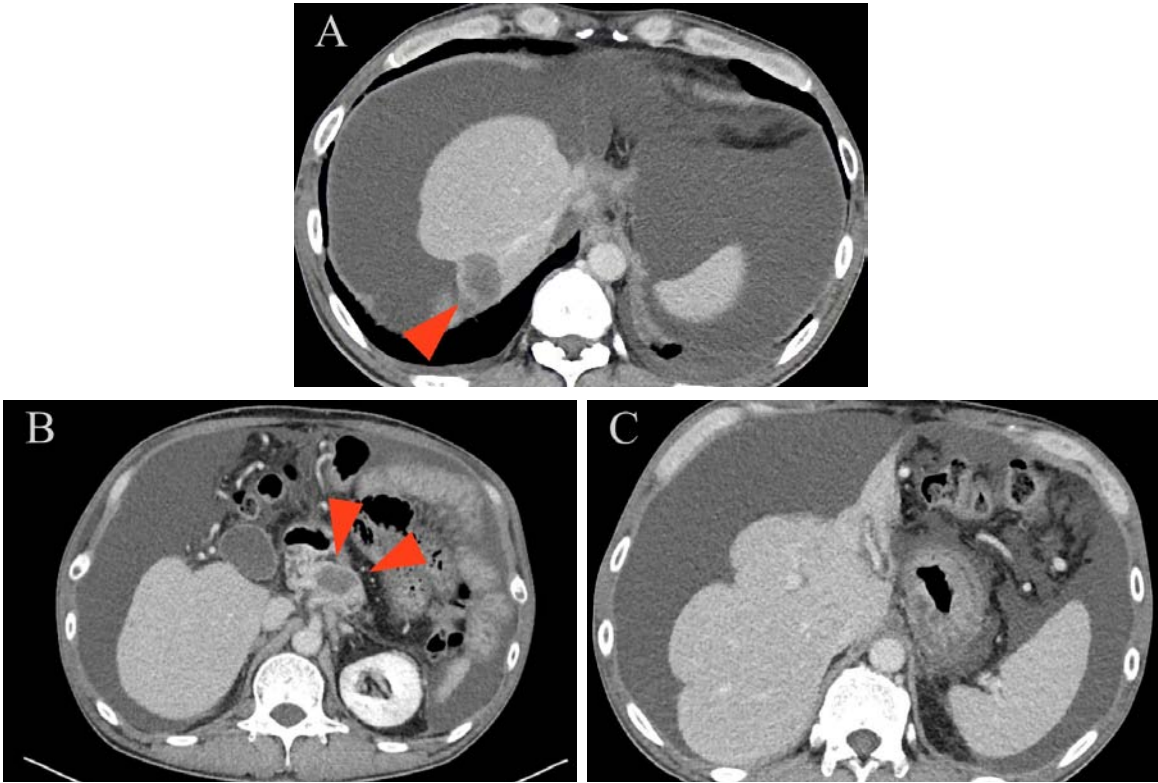


Figure 2. Abdominal CT findings 4 years and 7 months after the start of chemotherapy. A: Recurrence of liver metastasis was seen in S7 region and tended to increase (arrowhead). B: There was also an increase in peripancreatic mesenteric lymph node metastasis (arrowhead). C: Ascites was markedly increased and abdomen was also noticeably distended.

Table 2. Body temperature and blood pressure before and after CART

	Before reinfusion	During reinfusion	After reinfusion
Body temperature (°C)	36.93 ± 0.40	36.88 ± 0.50	36.91 ± 0.66
Blood pressure (mmHg)			
systole	111.86 ± 15.74	112.14 ± 22.96	115.25 ± 19.05
diastole	75.79 ± 10.96	72.36 ± 12.85	71.08 ± 17.27

(mean ± SD)

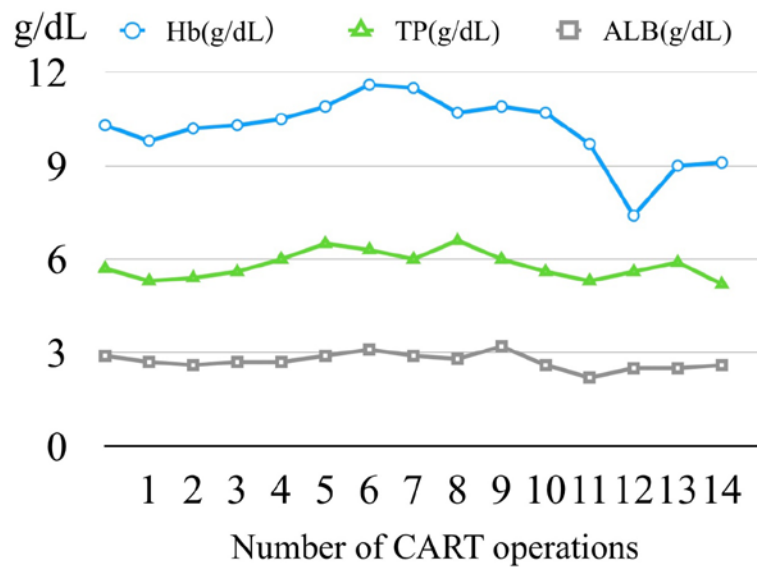


Figure 3. Progression of anemia was halted in the majority of CART procedures. Total-protein and albumin levels also passed without a significant drop.

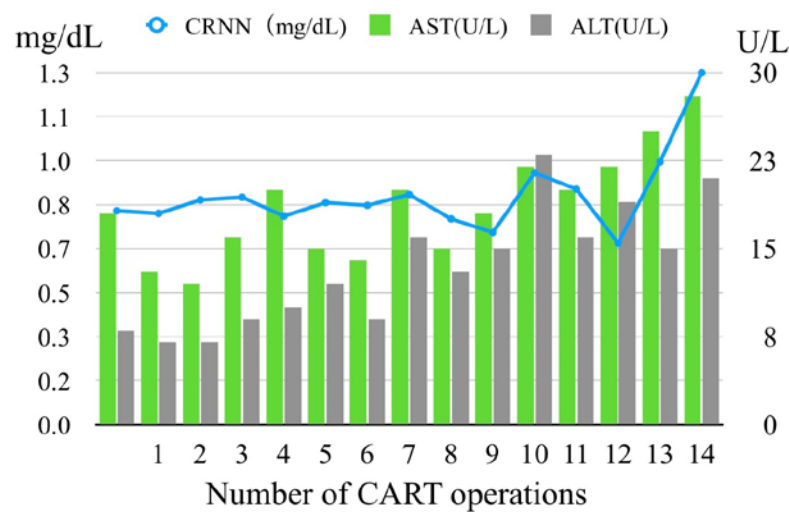


Figure 4. Creatinine was almost unchanged during the CART period. AST and ALT were not markedly elevated during the same period.

line of treatment. His remaining time was limited, but by improving his Activities of Daily Living (ADL), he was able to return in his job (construction industry), enjoy his hobbies and spend more time with his newborn grandchild.

After that, the patient's general condition gradually deteriorated due to chemotherapy-induced myelosuppression, appearance of disseminated intravascular coagulation signs, and decline in cognitive function. No further CART was performed. About a

month after the last CART he passed away with his family being at his bedside.

Discussion

Ascites retention has various causes, such as intra-abdominal malignancy, cirrhosis and infection²⁾. The frequency of malignant ascites is 53% for peritoneal dissemination, 13% for multiple liver metastases, and 13% for peritoneal dissemination plus multiple liver metastases. Peritoneal dissemination is the most common

cause⁴⁾. Symptoms of ascites retention include abdominal distension, anorexia and dyspnea¹⁾, which affect the patient's daily life. Diuretics are generally administered and these symptoms can be relieved by paracentesis⁵⁾, but since ascites contains many proteins, paracentesis alone may affect blood protein levels and circulatory dynamics³⁾.

CART involves taking ascites fluid from a patient, filtering it to remove unwanted components such as blood cells and cancer cells, and then concentrating the necessary components such as albumin and globulin. It is then administered intravenously back into the patient's body. It is effective in maintaining the patient's general condition¹⁾. The patient had a marked decrease in ADL due to malignant ascites caused by liver metastases and intra-abdominal lymph node metastases. He was in the construction business, but due to the short-term accumulation of massive ascites, he was unable to maintain a balance between work and treatment. Although the intervals of CART were short and frequent, subjective symptoms such as abdominal distension and pain were improved, and ADL was also improved with the decrease of weight and abdominal circumference. He was able to do heavy lifting and continue his own work, which was a great emotional support. In addition, the anemia did not progress during most of the CART period, and the nutritional status was maintained, which made it possible to continue the treatment. Although his remaining time was short, he was able to improve his QOL and lead a fulfilling life.

The major adverse effects associated with reinfusion are fever, chills, shock, and hypertension⁶⁾. The incidence of fever is particularly high at 20.5%⁶⁾. As for fever, it has been reported that prior oral administration of steroids or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can suppress fever³⁾. The patient was taking NSAIDs as analgesics, which may have suppressed the rise in body temperature. As for fluctuation in blood pressure, there is no clear evidence to prevent it, but at our hospital, re-infusion is performed at less than 100

ml/h. Other CART cases have been performed at that rate, and no extreme fluctuation in blood pressure has occurred. We believe that one of the reasons why we were able to perform CART repeatedly was that there were no notable adverse effects, which helped maintain safety and reassure the patients.

According to a previous report, when only paracentesis was performed, without intravenous injection of albumin, side effects including renal damage were common⁷⁾, and it was safe to treat refractory ascites with intravenous injection of albumin⁸⁾. However, since CART regenerates albumin from its own ascites and uses it, it can also contribute to reducing the use of albumin products⁹⁾. In this case, it was necessary to perform the procedure frequently in a short period of time, so it was appropriate to use CART in terms of saving medical resources.

Patients suffering from refractory ascites are often in the terminal phase. There is not much time left, but we have the impression that ADLs are severely reduced, and the time is often not used effectively. The patient was responsible for his work and wanted to work on his own without bothering others. He was also very close to his family and hoped to be able to spend as much time as possible with them. The introduction of CART was to meet this desire. We believe that CART is palliative care to improve quality of life and makes the rest of a patient's life more fulfilling. For that reason, its introduction should be actively considered.

(Conflict of interest: The authors indicated no conflict of interest.)

References

- 1) Matsusaki K, Ohta K, Yoshizawa A, et al. Novel cell-free and concentrated ascites reinfusion therapy (KM-CART) for refractory ascites associated with cancerous peritonitis: its effects and future perspective. *Int J Clin Oncol*. 16: 395-400. 2011.
- 2) Oey RC, van Buuren HR, de Man RA. The diagnostic work-up patients with ascites: current guidelines and

- future prospects. *Neth J Med.* 74(8): 330-335. 2016.
- 3) Maeda O, Ando T, Ishiguro K, et al. Safety of repeated cell-free and concentrated ascites reinfusion therapy for malignant ascites from gastrointestinal cancer. *Mol Clin Oncol.* 2(6): 1103-1106. 2014.
 - 4) B A Runyon, J C Hoefs, T R Morgan. Ascitic fluid analysis in malignancy-related ascites. *Hepatology.* 8(5): 1104-1109. 1988.
 - 5) Muhammad W Salf, Imran A P Siddiqui, Muhammad A Sohail. Management of ascites due to gastrointestinal malignancy. *Ann Saudi Med.* 29(5): 369-377. 2009.
 - 6) Hanafusa N, Isogai A, Ishihara T, et al. Safety and efficacy of cell-free and concentrated ascites reinfusion therapy (CART) in refractory ascites: Post-marketing surveillance results. *PLoS One.* 12(5): e0177303. 2017.
 - 7) P Gines, L Tito, V Arroyo, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology.* 94(6): 1493-1502. 1988.
 - 8) Watanabe M, Shiraishi K, Watanabe N, et al. The management of refractory ascites. *JJPH.* 12: 306-311. 2006 (Japanese).
 - 9) Utsugisawa T, Kobayashi R, Isoai A, et al. Efficacy of cell-free and concentrated ascites for autologous albumin products. *Japanese Journal of Transfusion and Cell Therapy*, Vol. 64. No. 5. 64(5): 631-640. 2018 (Japanese).