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Kim, Yongsik ; Ajiki, Tetsuo ; Ueda, Yasuhiro ; Yoshida, Yuko ; Takahashi, Tsuyoshi ; Fukuyama, Hitoshi ; Fukuyama, Tsuyoshi ; Hori,…

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Reappraisal of a Renovated Cell-free and Concentrated Ascites Reinfusion Therapy for Malignant Ascites

YONGSIK KIM[1,2], TETSUO AJIKI[1,3], YASUHIRO UEDA[1], YUKO YOSHIDA[4], TSUYOSHI TAKAHASHI[4], HITOSHI FUKUYAMA[5], TSUYOSHI FUKUYAMA[5] and YUICHI HORI[6]

[1]*Department of Surgery, International Clinical Cancer Research Center, Kobe University Hospital, Kobe, Japan;*
[2]*Department of Palliative Care, Kobe Minimally Invasive Cancer Center, Kobe, Japan;*
[3]*Department of Surgery, National Hospital Organization Kobe Medical Center, Kobe, Japan;*
[4]*Department of Surgery, Mitsubishi Kobe Hospital, Kobe, Japan;*
[5]*Department of Surgery, Fukuyama Hospital, Akashi, Japan;*
[6]*Department of Biophysics, Kobe University Graduates School of Health Sciences, Kobe, Japan*

Abstract. *Background/Aim: Cell-free and concentrated ascites reinfusion therapy (CART) was established for refractory ascites and renovated CART (Keisuke Matsusaki (KM) -CART) has been recently developed especially for malignant ascites; however, the actual clinical efficacy of KM-CART has been rarely reported. Patients and Methods: We performed 226 KM-CART procedures in 104 patients with malignant ascites in three hospitals from August 2013 to September 2018. Medical records were retrospectively reviewed for ascites data, related complications, symptoms before and after each CART and prognosis after the first CART. The modified Glasgow Prognostic Score (mGPS) was reviewed before every procedure, as an indicator of nutritional status. Results: Pancreatic cancer was the most common indication for the KM-CART procedure, followed by gastric cancer, hepatocellular carcinoma, ovarian cancer, and cholangiocarcinoma (five major diseases). The 50% survival times of these five major diseases after the first procedure were 25, 39, 31, 49, and 33 days, respectively. The mean survival time for all patients was 73.5 days, and 75.6 days for those with the five major diseases. All patients experienced symptomatic relief, and complications were rare. Repeated KM-CART was performed in 47.1% of the patients, most often in those with ovarian cancer (66.7%). Regarding the mGPS at the first CART procedure, 89% of patients were in the group with the poorest nutritional status. Patients who underwent KM-CART three or more times had longer survival than those who were treated once or twice. Conclusion: Repeated KM-CART provides a survival benefit for patients with malignant ascites, even in cases of poor nutritional status.*

Correspondence to: Tetsuo Ajiki, Department of Surgery, National Hospital Organization Kobe Medical Center, Nishiochiai, Suma-ku, Kobe 654-0155, Japan. Tel: +81 787910111, Fax: +81 787915213, e-mail: ajiki@med.kobe-u.ac.jp

Key Words: Renovated cell-free and concentrated ascites reinfusion therapy, KM-CART, Modified Glasgow Prognostic Score (mGPS), prognosis, cumulative survival rate.

Cell-free and concentrated ascites reinfusion therapy (CART) was established for refractory ascites and reported by Inoue *et al*. in 1977 (1). Ito *et al*. reported that, among 37 patients receiving CART, various symptoms related to malignant ascites, especially fatigue, improved within the 24-h period following CART (2). Recently the number of reports evaluating the efficacy of CART for malignant ascites has increased (3-8). CART not only improves the symptoms caused by refractory ascites, but also was reported to enable the resumption of anticancer drug treatment by significantly raising the serum protein level and increasing the urine volume of patients with malignant ascites (9). In cancer therapy, the combination of CART with followed chemotherapy is safe and could be a treatment option for malignant massive ascites (10, 11). However, with malignant ascites, during CART procedure the hollow fibers in the filtration unit were immediately clogged by fibrin, mucus, and cellular components, leading to a sudden increase in perfusion pressure (12).

For this difficulty in managing malignant ascites, Matsusaki *et al*. developed a renovated CART system, so called KM-CART. The patent of the system was filed in 2008 (No. JP5249973), and this system was called KM-CART after the developers, 'Keisuke Matsusaki' and 'Kuraray Medical' (12). This renovated system has a simpler circuit and uses an external pressure system, with a membrane cleaning function (13). This system mechanically cleans the membrane by the flow of physiological saline from the inner space to the outer

space of the hollow fiber when the filtration function deteriorates due to the attachment of cellular components to the fiber. KM-CART has made it possible to purify large volumes of malignant ascites, which is rich in cellular and mucous components and contains more than 20 liters of fluid, repeating the treatment with a lower filtration speed. Although few papers have reported the outcomes of patients treated with KM-CART, Matsusaki *et al*. have reported its efficacy for alleviating clinical signs/symptoms (12). The general status of patients improves with treatment and improvement of the Quality of Life could be expected. Although long-term survivors and cases of treatment cessation have been reported, careful selection is necessary for the application of KM-CART. However, there are few prognostic data for KM-CART and the repeat rate in various cancers, in clinical settings, is unclear.

The purpose of this study was to review retrospectively the clinical course of patients with malignant ascites after KM-CART, and to reveal the prognosis and repeat rate of KM-CART, according to the primary disease. To investigate the association between a patient's nutritional status before treatment and prognosis, we analyzed the modified Glasgow Prognostic Score (mGPS) as an indicator of nutritional status before each CART procedure; this has been reported to influence the prognosis in various cancers (14-18).

Patients and Methods

Patients. We analyzed the records and clinical courses of 104 patients, who underwent KM-CART therapy at Mitsubishi Kobe Hospital between October 2013 and June 2017, and at Fukuyama Hospital and Kobe University Hospital, International Clinical Cancer Research Center, between July 2017 and September 2018. Treatment criteria included the following, Performance status <2, Total bilirubin <5.0 mg/dl, Creatinine <2.0 mg/dl, no serious cardiopulmonary complication, and Hemoglobin >8.0 g/dl. Transfusions of 280-560 ml red cell components were given to patients with Hb below 8.0 g/dl, before each procedure. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Kobe University Hospital (#B100010-I).

Procedures. Each patient was admitted to hospital a few days before KM-CART and evaluated by a blood biochemical examination, before and after each procedure. Chest and abdominal radiography and computed tomography were evaluated. After confirmation by abdominal ultrasonography, each patient was punctured under local anesthesia. Ascites was drained through a catheter (14G, 50 cm; Argyle LCV-UK Catheter Kit; Covidien, Dublin, Ireland). During peritoneal drainage, 500 to 1,000 ml of acetated Ringer's solution with 10mg of prednisolone sodium succinate was continuously drip-infused, and the patient's vital signs, percutaneous oxygen saturation (SpO2), and signs /symptoms were monitored. As far as possible, the ascites was drained into a collection bag by intraperitoneal pressure, at a flow rate of 2.0-3.0 l/h. The ascitic fluid was immediately filtered using the KM-CART system equipped with AHF-MOW (polyethylene) and AHF-UP filters (Asahi Kasei Medical Co., Ltd., Tokyo, Japan).

Table I. *Patient characteristics*.

Variables	
Age, years	66 (38-86)
Sex, male/female	58/46
Kind of tumor	
Pancreas, biliary, liver	49
Gastrointestinal tract	31
Gynecology	14
Others	10
Serum laboratory data*	
Hb (g/dl)	10.3±1.8
T-Bil (mg/dl)	1.1±1.3
TP (g/dl)	6.2±0.8
Albumin (g/dl)	2.6±0.5
Creatinine (mg/dl)	1.1±0.6

Hb: Hemoglobin; T-Bil: Total bilirubin, TP: Total protein. *Data are shown as mean±SD.

The concentrated ascites was infused into the patient intravenously at a rate of 100 ml/h while monitoring the patient's signs/symptoms and hemodynamic parameters, which were recorded at 0, 5, 10, 15, and 60 min, and every 60 min thereafter. After confirming the absence of adverse events, the KM-CART therapy was completed successfully (12).

Parameters examined. The following parameters were analyzed in the 226 KM-CART procedures: (a) volumes of drained and concentrated ascites, (b) amount and ratio of recovered protein and albumin, (c) related complications and symptoms before and after each KM-CART, (d) laboratory data, including serum creatinine and albumin levels, total protein, and total bilirubin before and after KM-CART, and (e) prognosis after the first KM-CART procedure.

Modified Glasgow Prognostic Score. To estimate the relationship between nutritional status and practiced KM-CART procedures as well as prognosis, we determined the mGPS prior to each procedure. The patients were divided into four groups, according to their serum albumin and CRP values, as follows: Group A (Alb ≥3.5 g/dl and CRP <0.5 mg/dl), Group B (Alb <3.5 g/dl and CRP <0.5 mg/dl), Group C (Alb ≥3.5 g/dl, CRP ≥0.5 mg/dl), Group D (Alb <3.5 g/dl, CRP ≥0.5 mg/dl) (18).

Statistical analysis. Data are reported as the mean±standard deviation (SD). We measured overall survival from the date of the first KM-CART procedure to the date of death. Kaplan–Meier estimates were used in the analysis of survival data and the log-rank test was used to compare survival rates. *p*-Values of <0.05 are considered significant. All statistical analysis were carried out using the JMP 17 software (SAS Institute Inc., Cary, HC, USA).

Results

Patient demographics and clinical data. During the study period 104 patients underwent KM-CART. Patient characteristics in this study are shown in Table I. Mean age was 66 years and Hepato-biliary-pancreatic cancer was the most common.

Table II. *Primary disease, KM-CART procedure time and repeat rate.*

Primary disease	No. Pts	Total procedure time	Repeat times/No. Pts	Repeat rate, % (No. repeated pts / No. total pts)
Pancreatic cancer	23	43	5/1, 4/1, 3/3, 2/7, 1/11	52.2 (12/23)
Gastric cancer	21	38	5/1, 4/2, 3/1, 2/5, 1/12	42.9 (9/21)
Hepatocellular carcinoma	15	44	22/1, 3/1, 2/6, 1/7	53.3 (8/15)
Ovarian cancer	9	36	22/1, 3/1, 2/4, 1/3	66.7 (6/9)
Cholangiocarcinoma	8	17	6/1, 3/1, 2/2, 1/4	50.0 (4/8)
Colon cancer	5	9	4/1, 2/1, 1/3	40.0 (2/5)
Unknown primary cancer	5	7	2/2, 1/3	40.0 (2/5)
Breast cancer	4	6	2/2, 1/2	50.0 (2/4)
Gall bladder cancer	3	3	1/3	0 (0/1)
Uterine cancer	3	3	1/3	0 (0/1)
Appendix cancer	2	9	5/1, 4/1	100.0 (2/2)
Rectal cancer	2	5	4/1, 1/1	50.0 (1/2)
Lung cancer	1	3	3/1	100.0 (1/1)
Duodenal cancer	1	1	1/1	0 (0/1)
Uterine Sarcoma	1	1	1/1	0 (0/1)
Fallopian tube cancer	1	1	1/1	0 (0/1)
Total	104	226		47.1 (49/104)

Repeat time and outcomes of the KM-CART procedure. The detailed primary disease, procedure time and repeat rate of KM-CART are shown in Table II. Pancreatic cancer was the most common and the total number of patients with pancreatic cancer, gastric cancer, hepatocellular carcinoma, ovarian cancer, or cholangiocarcinoma was 76, accounting for 73.0% of all patients (76/104). Therefore, we consider these diseases as the "five major diseases of malignant ascites" in this study. As for the maximum repeated treatment times were five for pancreatic cancer, five for gastric cancer, 22 for hepatocellular carcinoma, 22 for ovarian cancer, six for cholangiocarcinoma, four for colon cancer, two for unknown primary cancer, two for breast cancer, five for appendix cancer, four for rectal cancer, and three for lung cancer. Among the pancreatic cancer patients, 12 could be treated more than twice, and the repeat rate was 52.2%. The repeat rate was 42.9% for gastric cancer, 53.3% for hepatocellular carcinoma, 66.7% for ovarian cancer, and 50.0% for cholangiocarcinoma. The mean±SD procedure interval time for all patients was 19±8 days.

After the KM-CART procedure, all patients had symptomatic relief. Grade III-IV complications defined according to the Clavien-Dindo classification (19) occurred only in two cases (1.9%, 2/104): one intra-abdominal hemorrhage in ovarian cancer and one acute renal failure in hepatocellular carcinoma. Figure 1 shows the first procedure in a gastric cancer patient with liver metastasis. This patient was able to sustain KM-CART therapy three times. After the KM-CART procedure, the abdominal distension disappeared quickly, and other subjective symptoms and the general condition of the patient improved.

Table III. *Outcomes of the 226 KM-CART procedures.*

Amount of drained ascites (l)	7.6±3.8
Amount of concentrated fluid (l)	0.5±0.3
Collected protein (g)	74.9±42.5
Collected albumin (g)	37.9±21.9
Ratio of protein recovery (%)	47.8±20.8
Ratio of albumin recovery (%)	51.0±22.4

Data are shown as mean±SD.

Ascites-related data from KM-CART procedures. Table III shows the ascites related data from the 226 KM-CART procedures. The mean total volume of ascites drained was 7.6 l, and the maximum volume of fluid drained during a single KM-CART procedure was 21.0 l, from an ovarian cancer patient. The mean total volume of concentrated fluid was 0.5 l. The mean amount of collected protein was 74.9 g, equivalent to 47.8% recovery ratio. Furthermore, the mean amount of albumin recovered was 37.9 g, equivalent to 51.0% recovery ratio.

Survival time after KM-CART. Figure 2 shows the cumulative survival curves of the patients with the five major diseases using the Kaplan–Meier method. The mean survival time for all 104 patients was 73.5 days, and for those with the five major diseases was 75.6 days. Ovarian cancer patients had the longest 50% survival time after the first KM-CART procedure, 49 days. The shortest 50% survival time was 25 days for pancreatic cancer patients. The 50%

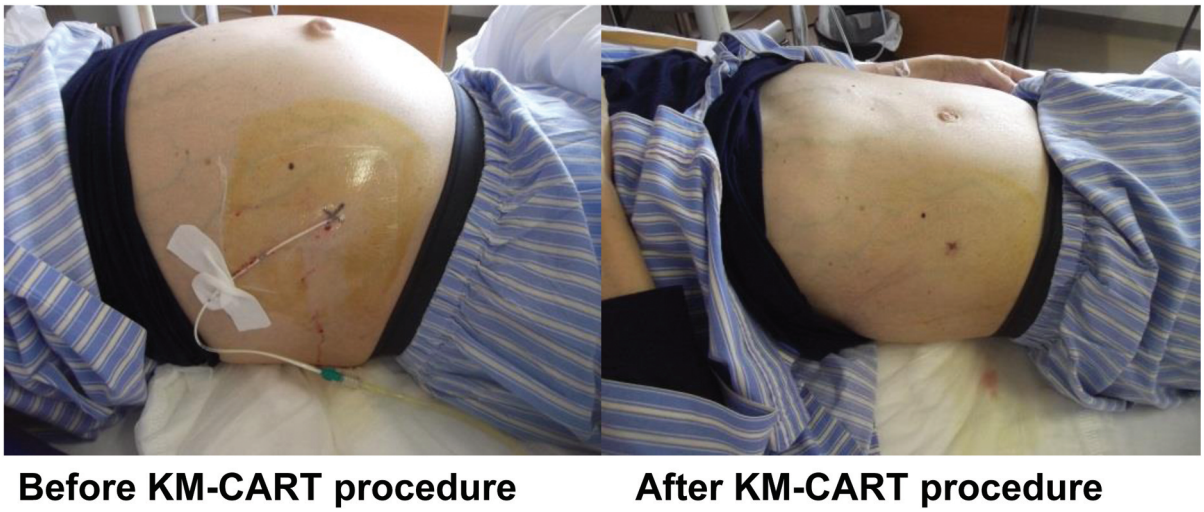

Figure 1. *Reduction of abdominal distension of a gastric cancer patient with liver metastasis. This patient was drained 5.78 l of ascites, including 138.7 g of protein and 57.8 g of albumin. Drip infusion concentrated 0.35 L of ascites, which is equivalent to 75 g of protein and 33.5 g of albumin. The ratio of protein recovery was 53.0% and albumin recovery was 58.1%.*

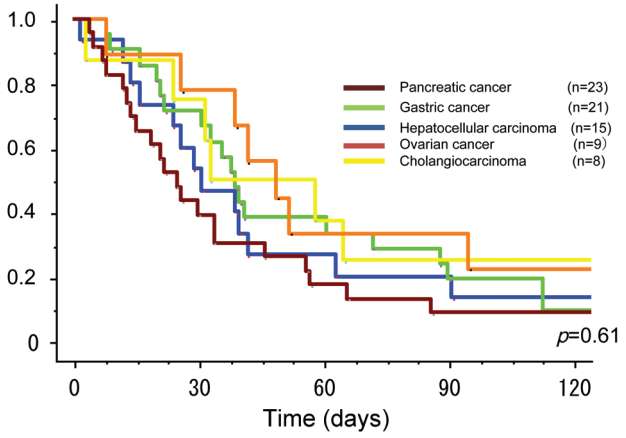

Figure 2. *The cumulative survival rate of patients with five major disease after the first KM-CART procedure (The Kaplan–Meier method).*

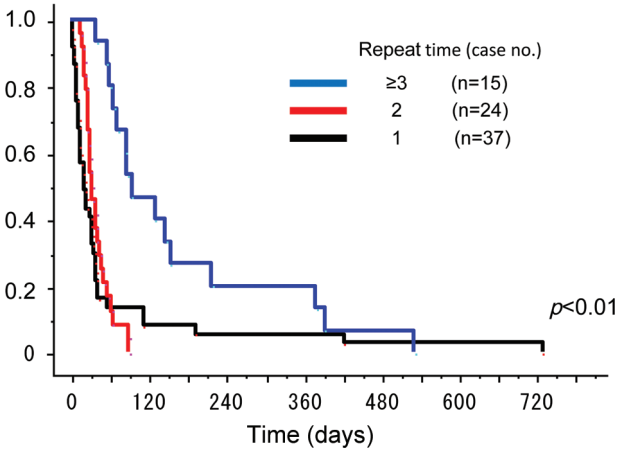

Figure 3. *The cumulative survival rate according to repeat time after the first KM-CART procedure.*

survival time was 39 days for gastric cancer patients, 31 days for hepatocellular carcinoma patients, and 33 days for cholangiocarcinoma patients.

Figure 3 shows the cumulative survival curves according to the repeat time of the KM-CART procedure for the five major diseases. The 50% survival time was 22 days for patients with a single procedure (37 patients), was 33 days for patients with two procedures (24 patients), and 88 days for those with three or more procedures (15 patients). Although the prognoses of patients with single and two KM-CART procedures were similar, patients who were treated three or more times had predominantly longer survival times than those who were treated once or twice ($p<0.01$).

KM-CART procedures and modified GPS. As for mGPS at the first procedure, there was no patient in Group A. There were five patients (one pancreatic cancer, two unknown primary cancer, one gastric cancer, one fallopian cancer) in Group B, and three patients (one pancreatic cancer, one hepatocellular carcinoma, one uterine sarcoma) in Group C. Of the 104 KM-CART cases, 96 (89%) were in Group D at the first procedure. Two patients with ovarian cancer

improved from Group D to B or C during treatment, but the other patients did not improve. The nutritional status of the patients was found to be poor, but the nutritional status of two patients (2/104, 1.9%) improved during treatment. One pancreatic cancer patient in Group B maintained the same score through three procedures, and this patient survived 218 days after the first treatment. Another pancreatic cancer patient in Group C at the first procedure had declined to Group D at the second procedure. This patient survived 46 days after the first treatment. There was no relationship between the mGPS score and number of KM-CART procedures, nor with the prognosis.

Discussion

To the best of our knowledge, this is the first report of the survival time and repeat rate of KM-CART procedures in a clinical setting. Regarding the prognosis of patients with malignant ascites, a retrospective review of 76 patients showed that median survival was 11.1 weeks from time of diagnosis and prolonged survival was found in patients with ovarian cancer (20). In another study by Garrison *et al*., it was demonstrated that tumors originating from the female reproductive system had the longest survival, with a mean survival of 19 weeks, and foregut adenocarcinomas had the poorest survival, with a mean survival of 10 weeks from the onset of ascites (21). In this study, of the five major diseases (accounted for 73% of all cases), ovarian cancer had also the longest 50% survival time (49 days), followed by gastric cancer, cholangiocarcinoma, and hepatocellular carcinoma. Pancreatic cancer had the shortest 50% survival time (25 days). Our results of survival time of patients with malignant ascites were shorter compared to those of previous reports because our data were from first KM-CART and data of previous reports were from the onset of ascites. Therefore, prognostic impact of KM-CART is thought to be unclear in this study, and KM-CART mainly provides symptomatic treatment.

Because KM-CART is often performed multiple times to improve the quality of life (12), we examined the repeat rate of this treatment. In this study, about half of the patients underwent repeated KM-CART therapy. Matsusaki *et al*. have already reported the improvement of treatment results and inspection data and concluded that KM-CART therapy had the "quality of best supportive care" for patients with malignant ascites (12). Maeda *et al*. suggested that higher albumin levels in ascites may lead to multiple treatments (22). Furthermore, Ito *et al*. reported that the presence of IL-10 in ascites was related to longer survival after CART, and the immunological environment of cancer-related ascites may reflect the outcome of CART therapy (23). From the results of this study, we consider the continuity of treatment to be critical. In this study, patients who were treated three or more times with KM-CART procedures had longer survival times than those who were treated once or twice. Thus, if possible, the longer the treatment period, the more benefit to the patient.

Nutritional status is important in enabling terminal stage patients to maintain their quality of life. Ayantunde *et al*. reported that low levels of serum albumin and total proteins are significant factors affecting survival (24). In particular, sarcopenia is an established adverse prognostic factor in cancer patients (18). In this study, pancreatic cancer patients, whose mGPS were in Group B and Group C at the first procedure, had long survival times, with maintenance of QOL. In addition, we found that two ovarian cancer patients, in mGPS Group D before their initial procedures were temporarily assigned to Group B and Group C after treatment. This suggests that a nutritional index, such as mGPS, may be useful as an indicator of the expected treatment effect and the possibility of continuation of treatment.

The outcomes of the 226 KM-CART procedures were almost the same as those in Matsusaki's report (12). Although this study does not assess the details of improvements of clinical findings, lower leg edema in many patients in our study improved promptly after KM-CART. Blood osmotic pressure is determined by the number of albumins per unit area, and albumin contributes the most to osmotic pressure. It would be extremely important and useful to restore albumin concentrations in order to improve intravascular circulatory failure, by collecting albumin from the ascites fluid and infusing it intravenously. Therefore, KM-CART is a very reasonable treatment for refractory ascites (12). This clinical study suggests that most patients with refractory ascites are malnourished and have hypoalbuminemia, but repeated KM-CART therapy may improve general condition by supplementing albumin recovered from the massive ascites.

Study limitations. First, this retrospective study was conducted only in three centers and was based on a small number of cases. A follow-up study is required to determine the survival time after treatment with prognostic surveys from various facilities. Secondly, some patients in this study were also receiving various cancer treatments in addition to KM-CART therapy. Of course, the availability of additional cancer treatment is such that there is a nutritional effect, and it is fully expected that the prognosis will be more favorable with good nutritional status. It is necessary to consider the post-treatment course of patients with and without such additional treatments.

Conclusion

We conclude that many malignant diseases with refractory ascites should be treated aggressively with multiple applications of the KM-CART procedure to achieve the good QOL and prognosis.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Yongsik Kim and Tetsuo Ajiki designed the study, analyzed, and interpreted the data. Yasuhiro Ueda, Yuko Yoshida, Tsuyoshi Takahashi, Hitoshi Fukuyama, and Tsuyoshi Fukuyama collected the data. Tetsuo Ajiki carried out the statistical analysis. Yuichi Hori checked the initial draft of the manuscript. This manuscript was critically revised and approved by all authors.

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