Adverse Effects of Cell Free and Concentrated Ascites Reinfusion Therapy (CART) for Malignant Ascites: A Single Institute Experience

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Research article

Keywords: Cell-free and concentrated ascites reinfusion therapy (CART), Malignant ascites, Adverse effects (AEs), Fever, Reinfusion rate

Posted Date: November 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-105381/v1

Version of Record: A version of this preprint was published at BMC Cancer on March 14th, 2022. See the published version at https://doi.org/10.1186/s12885-022-09298-6.

Abstract

Background: Cell-free and concentrated ascites reinfusion therapy (CART) is a strategy to improve hypoalbuminemia due to refractory ascites. CART has recently been applied in the treatment of cancer patients. This study was performed to assess the safety of CART in a single cancer institute.

Methods: We retrospectively reviewed 233 CART procedures that were performed for 132 cancer patients in our institute.

Results: The median volume of ascites before and after concentration was 4,720 and 490 mL (median concentration rate, 10.0-fold), The median amounts of total protein and albumin were 64.0g and 32.6g (median recovery rates, 44.9% and 49.0%), respectively. Thirty-three adverse events (AEs) were observed in 22 (9.4%) of 233 procedures; 30 of these events occurred after reinfusion. The most common reinfusion-related AEs were fever (13 events) and chills (10 events). Univariate analyses revealed no significant relationships between the frequency of AEs and age, sex, appearance of ascites, volume of harvested and concentrated ascites, the ascites processing rate (filtration and concentration), volume of saline used for membrane cleaning, amount of calculated total protein for infusion, or prophylaxis against AEs; the reinfusion rate >100 mL/h affected the frequency of AEs, regardless of the prophylactic use of steroids.

Conclusions: The observed AEs were mainly mild cytokine-related reactions after reinfusion, which were related to a reinfusion rate of >100 mL per hour. Although our study was retrospective in nature and undertaken in a single institute, this information may be helpful for the management of cancer patients with refractory malignant ascites using CART.

Background

Malignant ascites is a severe complication in the advanced cancer, including ovarian, stomach, breast, colon, lung, pancreas, and liver cancer. It is caused by peritoneal carcinomatosis that increases vascular permeability and lymphatic obstruction, and massive liver metastasis, which causes portal hypertension and hypoalbuminemia through the occlusion of hepatic vein, cirrhotic change and cachexia [1]. Ascites is classified into two categories, exudative and transudative ascites. Malignant ascites is usually exudative, but transudative ascites is also experienced when there is massive liver metastasis [2]. Once ascites is generated, the quality of life of cancer patients deteriorates through subjective symptoms such as abdominal fullness and pain, weight gain, appetite loss, nausea, constipation, leg edema and shortness of breath.

The most effective approach to treat ascites caused by cancers is tumor mass reduction by surgical resection and systemic chemotherapy. Because malignant ascites is commonly caused by tumors refractory to anti-cancer treatment, pharmacotherapy, such as diuretics, is not effective in many cases. Thus, its elimination is the most common pragmatic method to control the symptoms. In clinical practice, paracenteses, rather than peritoneovenous shunts, are preferred [3]. However, repeated paracenteses

induces hypoproteinemia through the elimination of proteins involved in ascites, which may lead to a worsening of edema and ascites, as well as fatigue.

Cell-free and concentrated ascites reinfusion therapy (CART), which has been approved by the Japanese national health insurance system, is a strategy to improve hypoalbuminemia due to refractory ascites [1]. The processing of ascites in CART is performed using two types of filters; the first filter is utilized to remove cellular and bacterial components from the ascites, and the second filter is to reduce the ascitic volume by eliminating the liquid component, resulting in the self ascites-derived fluid with concentrated proteins. The first report on CART in Japan was published in 1977 [4]. CART was initially applied in the treatment of refractory ascites in liver cirrhosis [5]. It has also been applied for malignant ascites [1].

CART itself is expected to improve ascites-associated symptoms (*e.g.*, abdominal distension, general fatigue, dyspnea and loss of appetite) as a palliative therapy, as well as renal dysfunction, while retaining the use of albumin preparation [1, 6–9]. CART combined with chemotherapy has been reported to be associated with a survival advantage in comparison to chemotherapy alone [10–12]. CART was reported to improve sinusoidal obstructive syndrome after hematopoietic stem cell transplantation [13]. However, CART is associated with adverse events (AEs), including shock, hypotension, chest pain, abdominal pain, dyspnea and hyperammonemia at puncture and drainage, and fever, chill, shivering, nausea, hypertension and headache at reinfusion [8].

In this study, we reviewed the cases of cancer patients with malignant ascites who underwent CART in our institute, with a focus on AEs, in order to report the safety of CART.

Methods

Patients

This retrospective observational study analyzed 233 CART procedures, which were performed in 132 patients at National Cancer Center Hospital (NCCH) from April 2015 to September 2019.

Procedure of CART

We utilized a modified CART procedure, known as KM-CART, which employs an external pressure system using suction equipment and also utilizes filter membrane cleaning [9, 14]. Briefly, abdominal paracentesis was performed using a 14-G, 30-cm central venous catheter inserted into the abdominal cavity under ultrasonographic monitoring. Ascites was collected in a sterilized collection bag supplied with heparin (2500U for 3 liters of ascites) by gravity flow at the rate of 1.5 to 2 L/h. The filtration and concentration of ascites were performed using AHF-MOW and AHF-UNH (Asahi Kasei Medical Co., Ltd., Japan), respectively. The concentrated ascites was reinfused with or without the prophylactic administration of anti-allergic agents, including corticosteroids.

Data collection

The information related to the patient's background and their clinical course, such as age/sex, diagnosis, adverse events (AEs) at the time points of puncture/drainage and after the reinfusion, prophylaxis against AEs and the reinfusion rate of concentrated ascites were collected from medical charts. The information related to the processing (filtration and concentration) of ascites is also collected, such as the appearance of ascites (bloody, chylous or serous), the volume and concentrations of protein/albumin before and after the processing, the time required for the processing, and frequency of washing filtration membrane during the processing. AEs were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Ascites was classified according to the difference in the albumin concentration in the serum and ascites (serum-ascites albumin gradient; SAAG); namely, high SAAG (equivalent to ≥ 1.1 g/dL) indicates transudative ascites, whereas low SAAG (< 1.1 g/dL) indicates exudative ascites.

Statistical analysis

All statistical analyses were performed in EZR, which is a modified version of R Commander designed to add frequently used statistical functions in biostatistics [15]. Differences between each group were compared using Fisher's exact test. All p-values were 2 sided and p-values of ≤ 0.05 were considered to indicate statistical significance.

Results

The patients' background characteristics are shown in **Table 1**. Notably, all patients suffered from malignant diseases. Among 132 patients, 41 (31%) received CART more than twice (Fig. 1). Fifty-two of 132 patients (39%) had gastric cancer, accounting for 79 out of 233 procedures (34%). The numbers of patients with other malignancies were as follows: colorectal cancer (n = 19; 14%) (66 procedures, 28%); pancreatic cancer (n = 20; 15%) (22 procedures, 9%); biliary tract cancer (n = 5; 4%) (7 procedures, 3%); renal cancer patients (n = 4; 3%) (16 procedures, 7%); malignant melanoma (n = 4; 3%) (6 procedures, 3%); breast cancer (n = 3; 2%) (4 procedures, 2%); liposarcoma (n = 3; 2%) (4 procedures, 2%); malignant mesothelioma (n = 3; 2%) (3 procedures, 1%); small intestinal cancer (n = 3; 2%) (3 procedures, 1%); and appendiceal cancer (n = 2; 2%) (5 procedures, 2%).

The harvested ascites was classified as exudative (142 procedures, 61%) and transudative (91 procedures, 39%). The summary of ascites processing through filtration and concentration is shown in **Table 2**. The median volumes of ascites before and after concentration were 4,720 (range, 500 − 14,150) mL and 490 (range, 55 − 1,550) mL, respectively. There was a correlation between these concentrations (R^2 = 0.5386) (Fig. 2A), and the median concentration ratio was 10.0 (range, 2.2 to 55.0) times. The volumes of harvested ascites tended to be correlated with the calculated amounts of total protein and albumin after concentration (R^2 = 0.50732 and R^2 = 0.42293, respectively) (Fig. 2B **and C**). The median concentrations of total protein and albumin in the concentrated ascites were up to 13.9 (range, 1.7–23.7) g/dL and 6.8 (range, 1.2–14.2) g/dL, respectively. Consequently, the calculated amounts of median total protein and albumin to infuse per procedure were 64.0 (range, 3.4–200.4) g and 32.6 (range, 1.5-127.7) g,

and the recovery rates of total protein and albumin in the concentrated products were 44.9 (range, 9.8–76.8) % and 49.0 (range, 11.6–84.1) %, respectively.

The AEs that were observed after reinfusion in this study are summarized in Fig. 3. Among 233 procedures, 33 events were detected in 22 procedures (9.4%). Regarding AEs related to reinfusion, 30 events occurred in 22 procedures (9.0%). Most reinfusion-related AEs were fever (13 events) and chills (10 events). Two events each of hypoxia and vomiting, and 1 event each of hypotension, dyspnea and urticaria were also experienced. Regarding AEs related to puncture/harvesting, 3 events occurred in 2 procedures (0.9%), where reinfusion-related AEs were also detected. These included pulmonary edema, hypotension and vomiting. There were two grade 3 events in all AEs, while all of the other events ranged from grade 1 to 2. All of these AEs, including the grade 3 events, were controllable either by conservative observation or transient medical treatment.

We then performed statistical analyses to clarify the factors related to these AEs (**Table 3**). Univariate analyses revealed that there was no statistically significant relationship between the frequency of AEs and age, sex, appearance (bloody, chylous or serous) and classification of ascites (exudative or transudative), volume of concentrated ascites, the processing ascites rate (filtration and concentration), the volume of saline used for cleaning the filter membrane, and prophylaxis against AEs. A high volume of harvested ascites (≥ 4,721 mL), and infusion of a large amounts of calculated total protein (≥ 64.1 g) and albumin (≥ 32.7 g) tended to be associated with an increased risk of experiencing AEs ($p = 0.051$, 0.051 and 0.075, respectively). Additionally, the reinfusion rate of concentrated ascites (≥ 101 mL/h) showed a statistically significant relationship with the occurrence of AEs in the analysis of 228 procedures. It still showed statistical significance when the analysis was limited to infusion with the prophylactic use of steroids (equivalent to ≥ 100 mg hydrocortisone) (196 procedures).

Discussion

The main purposes of CART in cancer treatment is to ease the discomfort derived from refractory ascites as a palliative treatment. Thus, the adverse effects related to CART, especially those with subjective symptoms, should be minimized in patients receiving the best supportive care. The current study showed that AEs were observed in 9.4% of 233 procedures. These were mainly mild and tolerable symptoms, as cytokine related-reactions, probably through the reinfusion of excessive amounts of cytokines contained in the ascites. They tended to be caused by the infusion of large quantities of proteins. It is therefore recommended that concentrated ascites be reinfused at a rate of < 100 mL/h, irrespective of prophylactic steroid administration.

AEs related to puncture/harvesting and reinfusion developed at the same frequency as seen in a previous multicenter study [12]. In the overall CART procedure, the most common AEs were fever and fever-related symptoms, such as chills after the reinfusion of concentrated ascites. The frequency of fever in this study, 5.6% (13 events), was comparable to that in previous studies, 5–16.4% [8, 11, 16, 17]. The average increase in body temperature was reported to be 0.1–0.44 °C [1, 9–11, 18]. Although a multi-center study

showed that the risk of fever did not differ according to the conditions of reinfusion, such as the amount of reinfused ascites/protein or the speed of reinfusion [8], our study suggested that the reinfusion of larger amounts of protein may increase the risk of fever; this was similar to the finding of another report that analyzed patients with gynecologic cancer [16]. The multi-center study included cases of transudative ascites due to liver damage, such as liver cirrhosis and hepatic carcinoma. It is therefore hypothesized that fever may occur due to the enriched inflammatory cytokines in concentrated ascites derived from carcinomatous peritonitis. The ascitic concentration of inflammatory cytokines (e.g., IL-6, IL-8 and IL-10) did not have a significant correlation with the changes in body temperature [19]. Additionally, IL-6 in the ascites decreased in the process of filtration and concentration [20]. The exact causes of fever still require investigation.

Puncture/harvesting-related AEs were reported to be less frequent, occurring in 2.5% of procedures in the previous multi-center study, and 0.9% of the procedures in the present study (2 of 233 procedures). The AEs in our study included pulmonary edema, which might be caused by inflation of lungs due to elimination of a large amount of ascites, and hypotension, which might be caused by extravascular defluvium of the blood plasma component. The volume of harvested ascites in these 2 procedures was more than the median in this study, 6,665 mL and 11,535 mL, but improved with transient medical treatment. This could be life-threating, as it could injure vital organs and systems, and the severity might be dependent on the volume of harvested ascites, in addition to the general condition of each patient. Thus, appropriate management of patients, including careful observation and prompt treatment, are required when performing CART, especially when a large volume of ascites is harvested.

In order to avoid AEs, such as cytokine related-reactions, as well as volume overload, the manufacturer's protocol recommends an ascites reinfusion rate of 100 to 150 mL/h. In most cases, reinfusion was performed after the prophylactic administration of corticosteroids for AEs, because steroids have been shown to be effective for inhibiting body temperature elevation in CART [8, 18]. However, AEs occasionally occurred, even with steroid prophylaxis. The finding in this study, that a reinfusion rate of $\leq$ 100 mL/h reduced AEs was consistently observed, regardless of the presence of steroid prophylaxis, suggesting the necessity for a stricter guideline regarding the reinfusion rate. CART has recently been applied for more cancer patients, who may have exudative ascites [1]. Although our study was retrospective in nature and performed in a single institute, this information may be helpful for the management of cancer patients.

One of the criticisms of our study was the low recovery rate of total protein and albumin in the processing of ascites (44.9 and 49.0%, respectively). In the modified CART (KM-CART) procedure, the recovery rates of albumin and globulin in 11 cancer patients were reported to be 71.1 ± 9.6% and 57.6 ± 7.1%, respectively, without membrane cleaning [14], while the protein recovery rate was 40.7 ± 14.0% in 4781 procedures with membrane cleaning [9], which were comparable to the data in this study. Frequent membrane cleaning therefore reduced the recovery rates of total protein and albumin. In addition, all patients in our study suffered from cancer. A multicenter study revealed that the lowest and middle tertile procedures of the recovery rate (47.3 ± 11.1%, 70.0 ± 6.0%) included a higher proportion of patients with exudative ascites (64.5%, 66.7%) and ascites with higher protein levels (3.6 ± 1.8 g/dL, 2.9 ± 1.4 g/dL),

which was in sharp contrast to the highest tertile (89.8 ± 6.7%), included a lower proportion of patients with exudative ascites (32.4%) and demonstrated ascites with lower protein levels (2.2 ± 1.4 g/dL) [8]. The background of ascites in our study was similar to the lowest to middle tertiles rather than the highest tertile. Accordingly, our recovery rate was considered to be reasonable and realistic.

Fever is a transient and mild AE in CART; however, its management is still important and valuable because CART is usually performed as a palliative therapy [1, 11]. Especially in cancer patients, the characteristics and contents of reinfused concentrated ascites vary according to those of the original ascites and modification through the CART procedure. It is therefore difficult to precisely perform a case-control study on CART for advanced cancer patients. Although the progress based on our findings might be limited, the accumulation of these findings will improve the strategy for CART, which is becoming increasingly important for relieving the discomfort associated with refractory ascites in cancer patients.

Conclusion

In conclusion, the CART, a palliative therapy established to relieve ascites-associated symptoms by the re-use of collected ascites, was found to be a safe treatment strategy. Most AEs were mild and tolerable cytokine-related reactions, such as fever and chills, that were mainly evaluated as grades 1 to 2, and which may be able to prevent a reinfusion rate of no more than 100 mL per hour. Although this study was retrospective in nature and carried out at a single institute, this information may nevertheless be helpful in the management of cancer patients with refractory malignant ascites using CART.

Abbreviations

AE
adverse events; CART:cell-free and concentrated ascites reinfusion therapy; serum-ascites albumin gradient; SAAG

Declarations

Acknowledgements

We are deeply grateful to Dr. Akira Kawai, Dr. Naoya Yamazaki, Dr. Jun Itami and Dr. Takaki Yoshikawa for their contribution of CART cases.

Authors' contributions

M.T. designed the study, engaged in inspection, prepared data file, collected clinical data, performed data analysis and wrote the manuscript. Y.A. designed the study, engaged in inspection, prepared data file and collected clinical data. Mi.K. assisted in writing the manuscript. R.T. designed the study conception. R.O., Y.Kas., N.I., Mo.K., S.N. and S.T. engaged in inspection and interpreted data. Ke.K., N.B., Y.Kan., T.O., H.F., K.Y., H.I. and E.S. provided medical care to CART patients and assisted in writing the manuscript. Ki.K.

was responsible for service at Department of Laboratory Medicine and interpreted data. H.M. designed the study conception, was responsible for service at Department of Laboratory Medicine, interpreted data, wrote the manuscript and provided administrative support for the study.

Funding

Not applicable

Availability of data and materials

Data are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by Institutional Review Board of National Cancer Center (#2019-053). The Institutional Review Board decided that individual written or verbal consent could be waived because of the retrospective and observational nature of the current study.

Consent for publication

This study does not contain individual data of person.

Competing interests

Dr. Matsushita reports a R&D commission fee from Asahi Kasei Medical. Dr. Kato reports research funds from ONO, MSD, Shionogi, Merck Biopharma, Oncolys Biopharma, Beigene, outside the submitted work. Dr. Okusaka reports grants and personal fees from ONO Pharmaceutical, Bristol-Myers Squibb, Eli Lilly, Eisai, Dainippon Sumitomo Pharma, Taiho Pharmaceutical, Pfizer Japan, Bayer Yakuhin, Chugai, Yakuruto Honsha, Zeria Pharmaceutical, Daiichi Sankyo, MSD, grants from Kyowa Hakko Kirin, Nano Carrier, Baxter, personal fees from EA Pharma, FUJIFILM RI Pharma, Celgene, Teijin Pharma, Shire, AbbVie, Takeda Pharmaceutical, Meiji Seika Pharma, Mundipharma, Nippon Servier, Nippon Shinyaku, outside the submitted work. The other authors declare no conflicts of interest in association with the present study.

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Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Figure 1

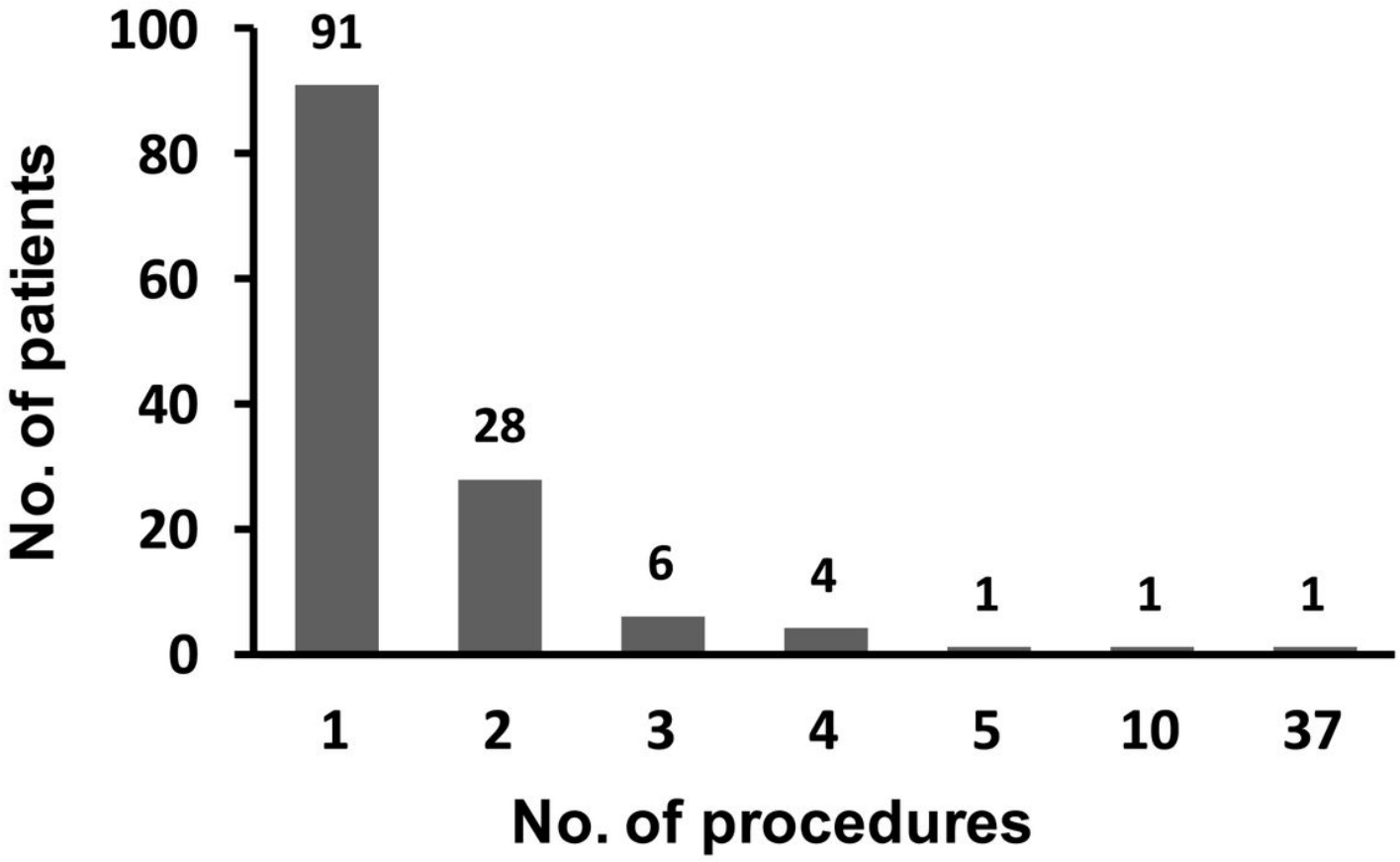

Figure 1

Total number of CART procedures in each patient.

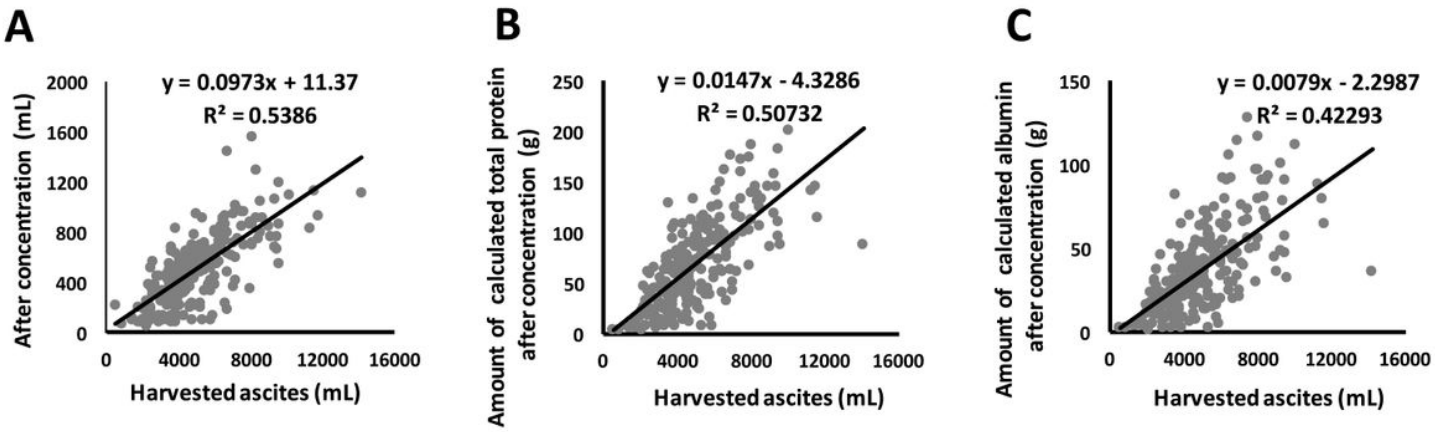

Figure 2

Relationship between the volume of harvested ascites and total protein/albumin content. A. The relationship between the volume of harvested ascites and volume after concentration. B. The relationship between the volume of harvested ascites and the amount of calculated total protein after concentration.

C. The relationship between the volume of harvested ascites and the amount of calculated albumin after concentration.

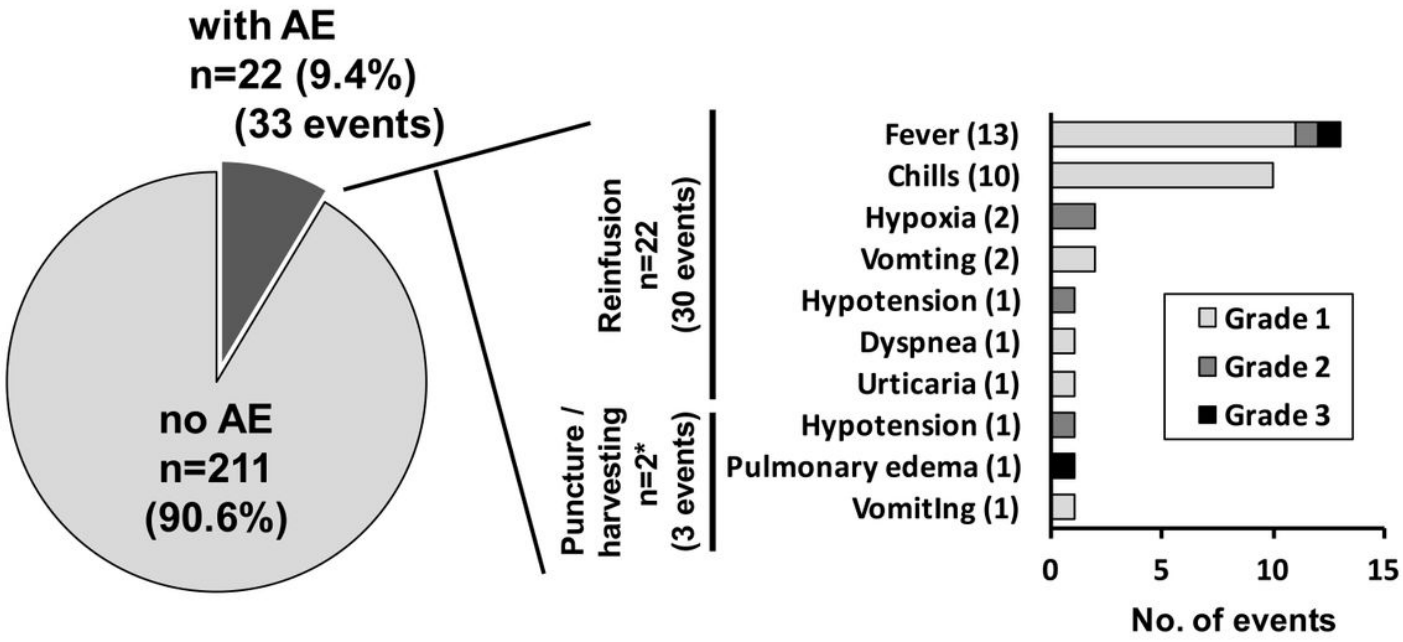

Figure 3

Adverse effects of CART therapy. * AEs related to reinfusion also occurred in these 2 procedures.

Supplementary Files

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