Evaluation of the performance, operability, and safety of Plasauto μ, a new type of machine for cell-free and concentrated ascites reinfusion therapy, in a postmarketing clinical study

Midori Hasegawa1 | Hiromichi Matsushita2 | Kensei Yahata3 | Akira Sugawara4 | Yoshitaka Ishibashi5 | Ryoko Kawahara6 | Yoshifumi Hamasaki7 | Hitoshi Kanno8 | Sachie Yamada9 | Norio Nii9 | Masao Kato9 | Atsushi Ohashi10 | Shigehisa Koide1 | Hiroki Hayashi1 | Yukio Yuzawa1 | Naotake Tsuboi1

1Department of Nephrology, Fujita Health University School of Medicine, Toyoyake, Aichi, Japan
2National Cancer Center Hospital, Chuo-ku, Tokyo, Japan
3Japanese Red Cross Osaka Hospital, Tenno-ku, Osaka, Japan
4Shizuoka General Hospital, Aoi-ku, Shizuoka, Japan
5Japanese Red Cross Medical Center, Shibuya-ku, Tokyo, Japan
6The Cancer Institute Hospital of JFCR, Koto-ku, Tokyo, Japan
7The University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan
8Tokyo Women’s Medical University Hospital, Shinjuku-ku, Tokyo, Japan
9Center of Blood Purification, Fujita Health University Hospital, Toyoyake, Aichi, Japan
10Faculty of Clinical Engineering, Fujita Health University School of Health Sciences, Toyoyake, Aichi, Japan

Abstract
Cell-free and concentrated ascites reinfusion therapy (CART) is performed by collecting the ascites from the patient, followed by filtration and concentration. Thereafter, concentrated cell-free ascites is reinfused into the patient intravenously. The new type of machine, Plasauto μ, for managing the process of CART was launched onto the market. We have evaluated the machine through postmarketing clinical study in 17 patients with malignant ascites. The amounts of original and concentrated ascites were 3673 ± 1920 g and 439 ± 228 g, respectively. Recovery rates were acceptable regarding values of total protein, albumin, and IgG that were 55.6% ± 17.3%, 60.2% ± 20.8%, and 58.2% ± 20.5%, respectively. Recovery rates were positively associated with amounts of original ascites and negatively associated with total protein concentration. No adverse events related to the machine were observed. The new type of machine showed preferable performance in processing malignant ascites.

KEYWORDS
a new type of machine, ascites, cell-free and concentrated ascites reinfusion therapy, postmarketing clinical study, recovery rate
1 | INTRODUCTION

In recent years, cell-free and concentrated ascites reinfusion therapy (CART) has been widely used for malignant ascites in Japan [1–4]. This process is carried out by collecting the ascites from the patient followed by its filtration and concentration. The Filtration filter is used to remove cellular components and the concentration filter is utilized to concentrate the ascites. Thereafter, concentrated cell-free ascites is reinfused to the patient intravenously. Compared to the traditional therapy for malignant ascites by abdominal paracentesis drainage, CART is expected to improve the patients’ nutritional status [3]. However, CART is time- and labor-consuming compared to conventional drainage techniques. Especially, in cases of malignant ascites containing many cellular components, such as cancer cells and red blood cells, the CART process sometimes could not be continued due to clogging of ascites filtration and concentration filters. The new type of machine for CART, Plasauto μ, was developed to reduce the laborious nature of this process. It is equipped with the following functions: an automatic membrane washing of clogged filtration filters, self-regulation regarding filtration and concentration processes, auto adjustment for concentrated ascites amounts by measuring their weight, and an illustrated guidance on a screen to easily figure out the process. To evaluate filtration and concentration performance, operability, and safety of the machine, we performed a postmarketing clinical study for Plasauto μ.

2 | PATIENTS AND METHODS

2.1 | Study design

The participants were patients with refractory ascites of cancerous origins for whom attending doctors decided that CART was the appropriate treatment. The inclusion criteria were patients: (i) who underwent CART for refractory ascites of cancerous origins using Plasauto μ (Asahi Kasei Medical Tokyo), (ii) who were 20 years of age or older, and (iii) who provided written informed consent. Since the study aimed to evaluate the machine functions such as automatic membrane washing of clogged filtration filters, ascites with high concentration of cellular products was preferable. Therefore, the patients with liver cancer, gallbladder cancer, bile duct cancer, or pancreatic cancer were excluded from the study. Ascites from these patients tended to be transparent with low concentration of cellular products and expected to have lower frequency of filter clogging when utilizing CART. The primary endpoint was total protein recovery rate. The secondary endpoints were: (i) filtration and concentration performance: amount of processed ascites, concentration ratio of amounts of ascites, total protein concentration ratio, albumin recovery ratio, albumin concentration ratio, IgG recovery ratio, and IgG concentration ratio. (ii) operability: frequency of membrane washing of filtration filter, frequency of alarm, type of alarm, processing time (the total filtration and concentration time), and operating time (processing time and priming time). The calculation formula for each item was as follows: Recovery rate (%) = [Amount of total protein, or albumin, or IgG in concentrated ascites]/[Amount of total protein, albumin, or IgG in original ascites] × 100; Concentration ratio of amount of ascites = [Amount of original ascites/Amount of concentrated ascites]; Concentration ratio of solute = [Concentration of total protein, albumin, or IgG in concentrated ascites/Concentration of total protein, albumin, or IgG in original ascites]; and Achievement rate for concentration of ascites (%) = [Amount of concentrated ascites/Target amount of concentrated ascites] × 100.

2.2 | Procedure of CART

The ascites of the patient was collected from a drainage line to an ascites collection bag (FCB-01T, Asahi Kasei Medical) by gravity. The amount of original ascites was measured. The original ascites was filtrated and concentrated by the machine as described below. The concentrated ascites was then infused intravenously to the patient at a rate of 100–150 mL/h, which could have been adapted by the doctor according to the patient’s condition.

2.3 | Filtration and concentration of ascites

Schematic drawing of processing ascites is shown in Figure 1. At first, the disposables of an ascites filtration filter (AHF-MO), an ascites concentration filter (AHF-UP), a paneled tubing set (AF-MYU), and a concentrated ascites collection bag (FCB-03T) (all disposables are from Asahi Kasei Medical), were placed on the machine. Besides, saline solution (1.8 L) bag and a bucket for waste fluid were placed and then connected according to the guidance displayed on the machine’s screen. The whole circuit comprising filtration filter, concentration filter, and tubing set was then primed with saline solution,
\[ \text{FIGURE 1} \quad \text{Schematic drawing of processing ascites. (a) The circuit diagram of “filtration and concentration.” Original ascites is filtered through AHF-MO and concentrated by passing through AHF-UP. The flow of ascites is shown by the black line. (b) The circuit diagram of “membrane washing.” Saline flows into AHF-MO to wash the membrane. The flow of saline is shown by the black line. (c) The circuit diagram of “recirculation.” The flow of ascites is shown by the black line. The mode of “filtration and concentration” and “recirculation” is repeatedly switched by automatic control of the gravimeter and adjusted to be the final target concentrated ascites amount.}\]

\[ \text{TMP1} = 30 \text{ mm Hg}^* \quad \text{(AHF-MO Outlet pressure). TMP2} = \text{(AHF-UP Inlet pressure).}^* \text{Differential pressure by gravity caused by hanging the original ascites bag on the pole of the machine}\]

\[ \text{FIGURE 2} \quad \text{Schematic drawing of the automatic membrane washing procedure of the ascites filtration filter of Plasauto } \mu. \text{ TMP1} = 30 \text{ mm Hg}^* \quad \text{(AHF-MO Outlet pressure).}^* \text{Differential pressure by gravity caused by hanging the original ascites bag on the pole of the machine [Color figure can be viewed at wileyonlinelibrary.com]} \]
followed by leakage tests for both filters. These processes were automatically performed by the machine after pressing the screen key. The ascites collection bag filled with ascites from the patient was set to the machine and connected to the circuit. The operator inputted the total amount of the patient’s ascites, the target amount of the concentrated ascites, and the type of ascites whether bloody or nonbloody by visual evaluation. Other parameters including “upper limit level of TMP1 (30 mm Hg – [AHF-MO Outlet pressure]),” “pressure level for flow rate control start,” and “upper and lower restriction levels of the flow rate” were set to the default values of 350 mm Hg, 300 mm Hg, 50 mL/min, and 45 mL/min for nonbloody ascites and 100 mm Hg, 80 mm Hg, 50 mL/min, and 45 mL/min for bloody ascites, respectively. These values could be modified by the operator if necessary. Concentrating the ascites was then started by pressing the start key. The procedures of “filtration/concentration,” “membrane washing,” and “recirculation” were regulated automatically by the machine. The membrane washing procedure was automatically performed by the machine, if necessary. This occurred when the filtration flow rate reached the lower restriction level and TMP1 reached the automatic control start pressure level. The operating principle of membrane washing procedure is schematically shown in Figure 2. The final amount of concentrated ascites was adjusted by controlling the weighing scale of the machine to match the target concentrated fluid amount.

2.4 | Registered facilities

Registered institutions included Fujita Health University Hospital, National Cancer Center Hospital, Japanese Red Cross Osaka Hospital, Japanese Red Cross Medical Center, Cancer Institute Hospital of JFCR, Tokyo Women’s Medical University Hospital, and University of Tokyo Hospital.

2.5 | Ethics

The study protocol conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). This study was approved by the Ethics Committee of the Fujita Health University School of Medicine (HM19-362). All participants provided written informed consent prior to their inclusion in the study.

2.6 | Data management and statistics

Data management and statistical analyses were outsourced to the Mebix Corporation. In safety assessment, the analysis was performed to evaluate the participants whose ascites were processed by Plasauto μ at least once among those enrolled in the study. In all other evaluations, the Full Analysis Set was used for analysis. Continuous data were expressed as means and SDs. Differences in the recovery rate between bloody and nonbloody ascites, heparin in the bag and nonheparin in the bag, with and without membrane washing, alarm occurrence or not were analyzed using Student’s t test. Correlations between the two groups were assessed using the Pearson correlation coefficient. A p value less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Basis of the enrolled patients

Out of the 19 enrolled patients, CART was discontinued in two patients before the machine was used. Therefore, data of the patients (n = 17) were used in the evaluation. The basic information of the enrolled patients is summarized in Table 1. The enrolled patients included 4 males and 13 females, with a mean age of 65.5 ± 14.1 years. Their diseases were gastric cancer in six cases, colon and rectal cancer in four, caecum cancer in two, uterine cancer in two, peritoneal cancer in two, and ovarian cancer in one. The type of ascites was bloody in seven cases and nonbloody in 10. In seven cases, 5000 units of heparin were injected in their original ascites bag.

3.2 | Filtration and concentration performance

The procedure of CART in each patient is summarized in Table 2. The amount of original ascites and processed ascites were 3673 ± 1920 g and 439 ± 228 g, respectively. The concentration ratio of amount of ascites was 8.9 ± 2.8. Total protein, albumin, and IgG levels in the original ascites were 3.0 ± 1.2 g/dL, 1.4 ± 0.6 g/dL, and 621 ± 281 mg/dL, respectively. In contrast, total protein, albumin, and IgG levels in the concentrated ascites were 13.0 ± 4.0 g/dL, 6.4 ± 2.3 g/dL, and 2797 ± 1322 mg/dL, respectively. The recovery rates of total protein, albumin, and IgG were 55.6% ± 17.3%, 60.2% ± 20.8%, and 58.2% ± 20.5%, respectively. The concentration ratios of total protein, albumin, and IgG were 4.7 ± 1.5, 5.1 ± 1.8, and 5.0 ± 1.8, respectively. The achievement rate for concentration of ascites was 99.7% ± 11.1%. However, the ratios were widely distributed; four cases had achievement ratios less than 90% and more than 80%, while three cases had less than 120% and more than 110%.
Factors affecting the recovery rates

The factors affecting the recovery rates of total protein, albumin, and IgG are indicated in Table 3. The recovery rates were positively associated with the amount of original ascites and negatively associated with total protein in original ascites. Type of ascites evaluated as either bloody or nonbloody, heparin addition in the bag, existence of membrane washing procedure, or alarms during the procedure were not associated with the recovery rate.

Evaluation of operability

In evaluation of operability, two patients’ data were missed because the operation log data could not be obtained accidentally. The mean processing time was 120 min, and the mean total operation time was 144 min. Membrane washing of the ascites filtration filter was performed in seven cases: once in three cases, twice in one case, and thrice in three cases (Table 1). Alarms occurred in seven patients (Table 1). Total amount of ascites was processed in each of the 17 cases.

Evaluation of safety

One adverse event of stomach pain was observed in patient #5 (Table 1), when ascites was being collected through paracentesis before utilizing the machine. The process was continued and completed the therapy without further complications. No other adverse events such as elevation of body temperature related to the CART procedure were reported during the study.

DISCUSSION

All original ascites had been processed in each of the 17 cases, and automatic membrane washing was performed in seven cases. If the machine did not have an automatic membrane washing procedure, interruption of the therapy or reduced recovery rate might have been observed in these seven cases. The protein recovery rate as a primary endpoint was 55.6% ± 17.3%. This result was lower than that of a previous report by Hanafusa et al. [1] that revealed a value of 72.0% ± 18.1%. However, it was comparable to that reported by Yamada et al. [3]: 59% ± 23%. The protein recovery rate is thought to
| Case number | Original ascites | Concentrated ascites | Concentration ratio of amount of ascites | Recovery rate |
|-------------|-----------------|---------------------|----------------------------------------|---------------|
|             | Amount (g)      | TP (g/dL) | IgG (mg/dL) | Amount (g) | Target amount (g) | Achievement rate (%) | TP (g/dL) | ALB (g/dL) | IgG (mg/dL) | TP (%) | ALB (%) | IgG (%) |
| 1           | 1990            | 3.9       | 1.8        | 583        | 335         | 400            | 83.8        | 11.0       | 5.6       | 1665   | 5.9     | 47.5     | 52.4     | 48.1     |
| 2           | 2840            | 3.2       | 1.8        | 454        | 385         | —              | 12.5        | 7.5        | 6.9       | 1789   | 7.4     | 53.0     | 56.5     | 53.4     |
| 3           | 7293            | 2.4       | 1.0        | 779        | 745         | 750            | 99.3        | 16.8       | 6.9       | 5460   | 9.8     | 71.5     | 70.5     | 71.6     |
| 4           | 7137            | 2.4       | 0.9        | 802        | 820         | 800            | 102.5       | 15.5       | 6.0       | 5096   | 8.7     | 74.2     | 76.6     | 73.0     |
| 5           | 5165            | 3.7       | 1.9        | 704        | 653         | 550            | 118.7       | 18.0       | 10.2      | 3740   | 7.9     | 61.5     | 67.9     | 67.2     |
| 6           | 3890            | 2.0       | 1.2        | 392        | 400         | 390            | 102.6       | 12.6       | 7.5       | 2415   | 9.7     | 64.8     | 64.3     | 63.3     |
| 7           | 2205            | 2.6       | 1.2        | 570        | 195         | 230            | 84.8        | 9.7        | 4.9       | 2199   | 10.7    | 34.7     | 38.0     | 35.9     |
| 8           | 1500            | 4.6       | 2.5        | 897        | 75          | —              | 19.0        | 10.5       | —        | 3739   | 18.5    | 22.3     | 22.7     | 22.5     |
| 9           | 6207            | 0.3       | 0.1        | 43         | 672         | 800            | 84.0        | 2.1        | 1.0       | 399    | 8.9     | 78.6     | 112.2    | 104.2    |
| 10          | 3425            | 1.4       | 0.6        | 421        | 330         | 320            | 103.1       | 9.5        | 3.9       | 2940   | 9.7     | 69.9     | 66.9     | 71.9     |
| 11          | 3290            | 3.7       | 1.8        | 728        | 405         | 410            | 98.8        | 16.5       | 8.4       | 3156   | 8.1     | 54.9     | 57.4     | 53.4     |
| 12          | 3290            | 3.9       | 1.9        | 787        | 450         | 410            | 109.8       | 15.5       | 7.5       | 3317   | 7.3     | 54.4     | 54.0     | 57.6     |
| 13          | 3145            | 3.4       | 1.2        | 775        | 430         | 440            | 97.7        | 10.2       | 4.3       | 2325   | 7.3     | 41.0     | 49.0     | 41.0     |
| 14          | 1665            | 3.2       | 1.7        | 331        | 225         | 200            | 112.5       | 13.8       | 7.8       | 1411   | 7.4     | 58.3     | 62.0     | 57.6     |
| 15          | 2490            | 4.0       | 1.5        | 945        | 255         | 300            | 85.0        | 12.0       | 5.0       | 3025   | 9.8     | 30.7     | 34.1     | 32.8     |
| 16          | 1805            | 4.8       | 1.7        | 1121       | 255         | 250            | 102.0       | 14.4       | 5.7       | 3518   | 6.6     | 45.1     | 50.4     | 47.2     |
| 17          | 5880            | 1.9       | 0.9        | 216        | 835         | 750            | 111.3       | 11.1       | 5.6       | 1348   | 7.0     | 83.0     | 88.4     | 88.6     |

Mean ± SD 3673 ± 1920 3.0 ± 1.2 1.4 ± 0.6 621 ± 281 439 ± 228 467 ± 212 99.7 ± 11.1 13.0 ± 4.0 6.4 ± 2.3 2797 ± 1322 8.9 ± 2.8 55.6 ± 17.3 60.2 ± 20.8 58.2 ± 20.5

Abbreviations: ALB, albumin; CART, concentrated ascites reinfusion therapy; TP, total protein.
Correlation factor analysis for the recovery rates

This study has several limitations as one-armed observational study with small number of cases.
CONFLICT OF INTEREST
This study was financially supported by Asahi Kasei Medical Co., Ltd. There are no other conflicts of interest for this study.

REFERENCES
1. Hanafusa N, Isoai A, Ishihara T, Inoue T, Ishitani K, Utsugisawa T, et al. Safety and efficacy of cell-free and concentrated ascites reinfusion therapy (CART) in refractory ascites: post-marketing surveillance results. PLoS One. 2017;12(5): e0177303.
2. Ito T, Hanafusa N. CART: cell-free and concentrated ascites reinfusion therapy against malignancy-related ascites. Transfus Apher Sci. 2017;56(5):703–7.
3. Yamada Y, Inui K, Hara Y, Fuji K, Sonoda K, Hashimoto K, et al. Verification of serum albumin elevating effect of cell-free and concentrated ascites reinfusion therapy for ascites patients: a retrospective controlled cohort study. Sci Rep. 2019;9(1):10195.
4. Yamada Y, Yamaguchi A, Harada M, Kurasawa Y, Hara Y, Yamazaki D, et al. Protein concentration of refractory ascites in cancer patients is reflected by the presence and severity of peritoneal and liver metastasis. Ther Apher Dial. 2017;21(3):263–9.