Clinical Significance of Cell-free and Concentrated Ascites Re-infusion Therapy for Advanced and Recurrent Gynecological Cancer

TAEKO UEDA, MIYAKO MAEHARA, YOKO TAKAHASHI, NAOMI NAKAYAMA, HARUHIKO KONDO, KYOKO SHIROTA, TOSHIYUKI YOSHIZATO and SHINGO MIYAMOTO

Department of Obstetrics and Gynecology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

Abstract. Background: The management of malignant ascites is critical for the treatment of patients with advanced gynecological cancer. The purpose of this study was to assess the clinical significance of cell-free and concentrated ascites re-infusion therapy (CART). Patients and Methods: Adverse events, alterations in Eastern Cooperative Oncology Group performance status, serum albumin, body weight and abdominal circumference, and overall survival were examined in 22 patients with advanced gynecological cancer which were treated with CART. Results: Most of the adverse events were grade 1 or 2 fever. CART treatment had little effect on ECOG performance status and on levels of serum albumin. There was a significant decrease in body weight and in abdominal circumference post-treatment with CART, relative to pre-treatment (p<0.01). The overall survival rate was significantly prolonged in 14 patients after CART plus chemotherapy, as compared with eight patients after CART alone (p<0.01). Conclusion: CART may contribute to the improvement of quality of life and of survival in patients with advanced gynecological cancer.

In advanced gynecological cancer, especially in the case of ovarian, peritoneal and endometrial cancer, cancer cells spread extensively in the abdominal cavity, resulting in massive refractory ascites (1). Such refractory ascites when associated with peritonitis carcinomatosa cause severe abdominal distension, dyspnea, appetite loss and circulatory failure. Even a transient removal and re-infusion of refractory ascites leads to relief from severe symptoms, facilitation of oral intake, circulatory improvement and renewed determination of the patient to continue living and fight their disease (2). In addition, the subsequent chemotherapy can potentially eliminate the ascites and enable discharge of the patient from the hospital. The management of malignant ascites is a significant challenge in medical oncology. Current treatment strategies include diuretic therapy, paracentesis, peritoneal drains and venous shunts (3-5). However, there are no established evidence-based guidelines.

Cell-free and concentrated ascites re-infusion therapy (CART) for refractory ascites is carried out in the following four ways: i) Ascitic fluid is collected by abdominal paracentesis; ii) bacteria and malignant cells in the fluid are filtered off; iii) the autologous proteins are concentrated; and iv) the filtered and concentrated autologous ascitic fluid is re-infused into the patient’s vein. Britton first reported the efficacy of CART for patients with liver cirrhosis (6). Since then, CART has been applied to the treatment of refractory ascites in patients with conditions such as liver cirrhosis, congestive heart failure, nephrotic syndrome and malignancies (7-12). Nevertheless, CART has not been used widely for the treatment of refractory ascites in patients with cancer and there have been few reports concerning its safety and clinical efficacy (13, 14). Accordingly, the best treatment of cancer patients with refractory ascites using CART still needs to be established.

Advanced gynecological cancer and its recurrence frequently results in peritoneal carcinomatosis with refractory ascites. Therefore, the management of refractory ascites in the treatment of advanced gynecological cancer remains a key problem. The purpose of this retrospective study was to evaluate the safety and efficacy of CART and to assess the clinical significance of CART plus chemotherapy in patients with refractory ascites.

Materials and Methods

Patients. Fifty-seven sessions of CART were performed in 22 patients with advanced gynecological cancer at the Fukuoka University Hospital from June 2008 to September 2011. These patients consisted of 15 with ovarian cancer, 4 with peritoneal cancer and 3 with endometrial cancer. All patients were in a disease-
recurrent state and had already developed resistance to standard chemotherapy. Fourteen out of the 22 patients had undergone chemotherapy after CART.

**CART procedure.** We performed CART in cases where the three following conditions were fulfilled: i) any symptoms due to refractory ascites; ii) collected volume of peritoneal fluid was estimated at over 1000 ml; and iii) request for this treatment from the patient. In order to remove impurities, the ascites were filtered through columns of the AHF-MOW model. The filtered ascites were then concentrated using the columns of the AHF-UNH or AHF-UP models. All three columns were manufactured by Asahi Kasei Kuraray Medical (Tokyo, Japan). The concentration ratio was unified at 1/10. In compliance with the requirements of national Japanese Health Insurance, CART was not repeated within 14 days from the first CART session. If a patient’s symptoms, due to the presence of ascites, worsened within 14 days, simple paracentesis was undertaken.

**Study design.** The serum albumin levels, body weight, abdominal circumference and the Eastern Cooperative Oncology Group (ECOG) performance score were examined on the day of the CART procedure and on the following day. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, Version 4.0 grading system (15). The repeated interval in CART was defined as the mean time from one CART treatment to the next CART treatment. Overall survival was determined from the time of the first CART treatment until the date of death or the last follow-up evaluation.

**Statistical analysis.** Values mean±standard deviation. The Wilcoxon signed-rank test was used to examine the association between two categorical variables. The Mann-Whitney U-test was applied to check the significance of the repeated intervals in the CART procedure. Survival estimation was performed using the Kaplan–Meier method and the log-rank test. A p-value <0.05 was considered as being statistically significant.

**Results**

CART was performed 57 times in 22 patients with advanced ovarian or endometrial cancer. The average volume of ascites that was collected at each treatment session was 3290 ml (range=500-8200 ml). Before the beginning of CART, ECOG performance status (PS) in nine cases was 1, in 26 cases was 2, in 21 cases was 3 and in 1 case was 4. After CART, there was no change in PS in 52 cases and in three cases PS had improved from 3 to 2. In two cases, PS had worsened from 2 to 3. These results indicated that CART had little effect on PS.

There was no significant difference (p=0.08) in serum albumin levels pre- (2.34±0.64 g/dl) and post-CART (2.39±0.62 g/dl) (Figure 1). Post-CART, a significant decrease (p<0.01) in both body weight (49.7±8.8 kg) and in abdominal circumference (83.5±11.2 cm) was observed relative to pre-CART values (body weight 52.6±8.4 kg and abdominal circumference 90.2±9.7 cm) (Figures 2 and 3). Adverse effects of CART are listed Table 1. The total rate of occurrence of the adverse events was 47.4% (22/57). Fever was the most frequent adverse event in CART (18/57; 31.6%). Most of the adverse events were grade 1, and only two cases had grade 2 events (high fever). These results suggested that CART may be used for the treatment of refractory ascites without severe adverse events.

Repeated intervals (N=34) of 44.7±117.0 days in patients treated with CART plus chemotherapy were significantly longer (p<0.01) than those in patients treated with CART alone (N=23; 12.3±16.4 days) (Figure 4). Overall survival of patients after CART plus chemotherapy (14 intervals) was significantly prolonged (p<0.01) as compared with CART alone (eight intervals) (Figure 5). These results suggest that chemotherapy after the CART procedure had a favorable effect on the management of refractory ascites in patients with advanced gynecological cancer.

**Discussion**

In the present study, CART procedures were found to transiently ameliorate the circulatory dynamics and reduce a variety of discomforting symptoms in patients with refractory ascites. Such a temporary improvement in the general condition of patients with malignant ascites facilitated the safe delivery of cancer chemotherapy. Symptoms associated with malignant ascites included abdominal distention, abdominal pain, nausea, vomiting, dyspnea, appetite loss and dyspepsia. Treatment options for recurrent malignant ascites are limited, and include diuretics, serial paracentesis and peritoneovenous shunting. Therapeutic
paracentesis yields temporary relief in approximately 90% of patients with refractory ascites (4, 16). A significant reduction in serum protein levels is associated with therapeutic paracentesis (3, 17). Reportedly, in a case-series involving simple paracentesis, the mean time before repeated paracentesis is 10.4 days. In the present study, repeated paracentesis associated with the use of CART was needed every 12.3±16.4 days, which was a similar interval as the one reported by Becker et al. (4). However, no significant difference in serum albumin levels was found pre- and post-CART in patients with refractory ascites. Accordingly, it is plausible that the use of paracentesis with CART is sufficient therapy to maintain the circulatory dynamics for a few weeks.

Refractory ascites include a variety of inflammatory substances such as interleukins (ILs), which are produced by cancer cells and white blood cells (18). It has been reported that the re-infusion of concentrated inflammatory substances causes high fever (19). However, in our study 18 out of 57 cases (31.6%) displayed grade 1 or 2 fever, which was the most frequent adverse event during CART. In addition, these
adverse events had disappeared within 24 h in all cases. In the CART procedure, two types of filter membranes are used. The first filter membrane has a potential for completely removing cancer cells, white blood cells and some bacteria with a maximum pore size of 0.2 μm. The second filter membrane, with a pore size of 80 Å or 30000 molecular weight (MW) cut-off, has the capacity to concentrate serum molecules, including useful proteins such as serum albumin and globulin. Substances of less than 30000 MW, such as electrolytes, are not concentrated, and thus serum electrolyte imbalance should not be a concern here. This method has the shortcoming that substances with applicable MWs will always be concentrated. It is said that inflammatory cytokines, such as IL-6, are the causative agents of fever following CART; likewise endotoxin and fibrin are also purported to be causative agents. However, the causative agent(s) of fever following CART has yet to be definitively identified (8, 20). Fever is the most frequent adverse event, but clinically administered pre-medication, such as non-steroidal anti-inflammatory drugs, can successfully ameliorate it.

Increased microvascular permeability of the tumor vasculature is the main factor in malignant ascites formation. The ascite production correlates with the extension of neovascularization. Angiogenesis promoted by vascular endothelial growth factor (VEGF) is associated with fluid accumulation in human tumor effusion, and malignant ascites are accompanied by high levels of VEGF (21). Specific VEGF inhibitors and tumor necrosis factors inhibit the interaction between VEGF and its receptor, thus preventing malignant ascite formation (22, 23). In our study, the administration of chemotherapy after CART in patients with refractory ascites prolonged the overall survival, as compared with CART alone. In the near future, combinatorial chemotherapy after CART with molecularly targeted agents such as VEGF inhibitors, with or without conventional anticancer agents, may become one of the most favorable therapies for patients with refractory ascites in advanced gynecological cancer.

Acknowledgements

This work was supported by Grant-in-Aids for Scientific Research (C) (no. 23592470 and no. 23592469) from the Ministry of Education, Culture, Sports, Science and Technology (Tokyo, Japan) and by funds from the Kajihara Science and Technology Foundation (Fukuoka, Japan), from Kyowa Hakko Kirin Co. Ltd. (Tokyo, Japan) (S. Miyamoto), and from the Central Research Institute of Life Sciences for the Next Generation of Women Scientists, Fukuoka University (Shirota K).

References


