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Repeated Combined Chemotherapy with Cisplatin Lowers Carnitine Levels in Gastric Cancer Patients

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Keywords
Carnitine · Chemotherapy · Ciplatin · Nutrition · Gastric cancer

Abstract
Background/Aims: Carnitine plays an important role in the metabolism of fatty acids. It has also been reported that the administration of anticancer drugs may lead to reductions in serum carnitine levels due to decreased activity of organic cation transporter novel 2, which plays a role in the reabsorption of carnitine in the tubules of the kidney. We therefore studied the change in carnitine levels when chemotherapy was administered repeatedly to patients with gastric cancer. ***Methods:*** Ten patients with upper gastrointestinal cancer were enrolled in this study between December 2014 and August 2015. All patients were administered chemotherapy consisting of TS-1 and cisplatin every 3 weeks: 3 received it as adjuvant therapy post resection, the remaining 7 received it as treatment for unresectable tumors. Before the start of each chemotherapy cycle, serum was collected. ***Results:*** The mean total carnitine level was 54.5 ± 13.7 μmol/L prior to commencing chemotherapy; it was 46.7 ± 13.5 and 41.4 ± 14.8 μmol/L at the second and third cycles respectively. The total carnitine level was decreased in a statistically significant manner ($p = 0.0039$). The serum level of total protein and cholinesterase was also decreased significantly ($p = 0.0218$ and $p = 0.0418$). ***Conclusion:*** Carnitine levels decreased during repeated chemotherapy in patients with gastric cancer, and they are associated with the nutritional status.

Introduction

Carnitine is a vitamin-like substance present in trace amounts, synthesized from methionine and lysine in the kidney, liver, and brain [1]. It plays an important role in the metabolism of fatty acids [2].

Deficiencies of carnitine are reported to cause severe symptoms such as muscle weakness, fatigue, heart failure, and hyperammonemia [3, 4]. Furthermore, carnitine deficiencies have been reportedly associated with subjective symptoms in cancer patients [5, 6].

It has also been reported that the administration of anticancer drugs may lead to reductions in serum carnitine levels due to decreases in the activity of the organic cation

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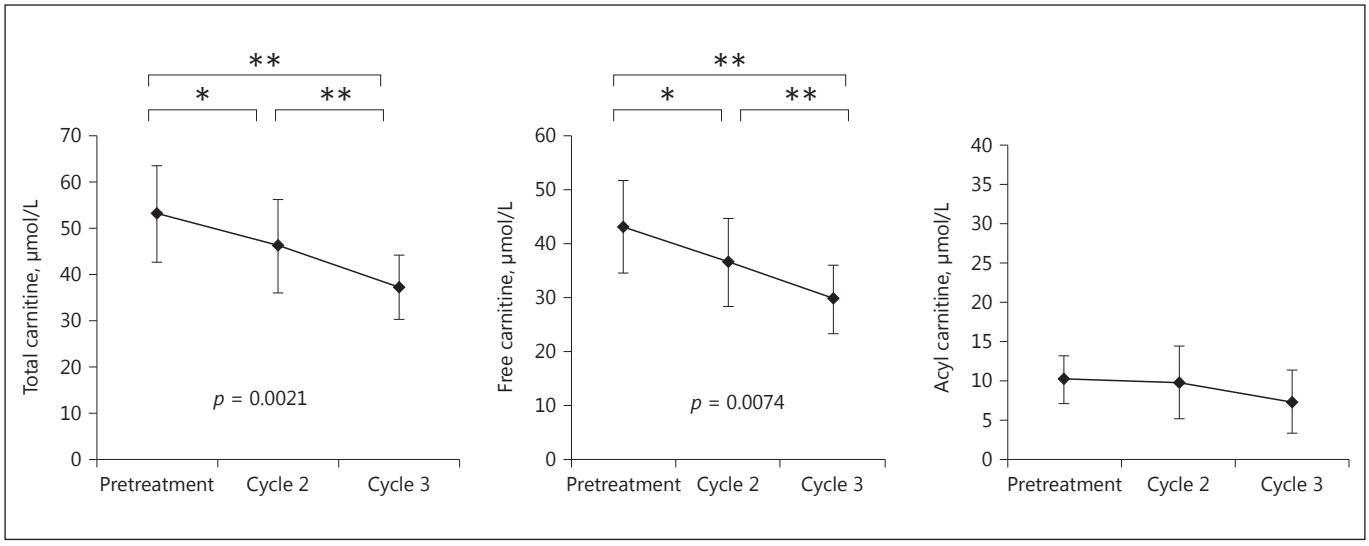

Fig. 1. Changes in serum carnitine level. * $p < 0.05$; ** $p < 0.01$.

transporter novel 2, which plays a role in reabsorption of carnitine in the tubules of the kidneys [7].

We therefore assumed that repeated chemotherapy might reduce carnitine levels significantly and be associated with nutritional disorders.

Patients and Methods

This study was proposed prospectively. Ten sequential patients (5 men, 5 women) with gastric cancer were enrolled in this study between December 2014 and August 2015. All patients were administered chemotherapy consisting of TS-1 (80 mg/m^2) and cisplatin (60 mg/m^2) every 3 weeks as they were all at stage IV of the disease. Three patients (women) received gastrectomy in stage IIIC and 7 patients were unresectable gastric cancer patients in stage IV according to UICC TNM classification. One day before the start of each chemotherapy cycle, serum was collected and analyzed for the level of total protein (TP), albumin (Alb), cholinesterase, and total cholesterol at the laboratory of Kawasaki Medical School Hospital. The level of total carnitine, acyl-carnitine, and free-carnitine was analyzed at an outsourced laboratory company (SRL Inc., Tokyo, Japan). Normal lower limits of total, free, and acyl carnitine level were more than 45.9, 36.7, and 6.2 μmol/L, respectively. The percentage of body muscle mass was measured using bioelectrical impedance analysis by a Body Water Analyzer (In Body S10, In Body Japan, Tokyo, Japan).

When the serum carnitine level decreased below the low normal range in this study, l-carnitine was administered as soon as the result was known.

This study protocol was approved by the Institutional Review Board of Kawasaki

Medical School (Approval No. 1855) and informed consent was obtained from all patients.

Statistical Analysis

Correlations between groups were determined by the chi-square test. All statistical calculations were performed with JMP® 10 software (SAS Institute Inc., Cary, NC, USA). A p value <0.05 was considered to be statistically significant.

Results

Three female patients received chemotherapy of TS-1 + cisplatin after gastrectomy, while the other 7 patients received it as treatment for their unresectable cancer. All patients received more than 2 cycles. The mean age was 63.8 years. Five patients were able to undergo evaluation for more than 4 cycles.

Carnitine

Total carnitine and free-carnitine levels were significantly reduced from 53.2 and 42.9 to 37.2 and 29.8 μmol/L ($p = 0.0021$ and $p = 0.0074$), respectively, at the beginning of chemotherapy and before the third cycle. The acyl-carnitine level also decreased from 10.3 to 7.4 μmol/L but did not reach statistical significance (Fig. 1). The level of carnitine in 4 patients decreased below the accepted lower limit; therefore, they were administered l-carnitine (l-cartin® FF tablet, Otsuka, Japan) after 2 cycles in this study. Five patients could be treated for more than 4 cycles without administration of the l-carnitine.

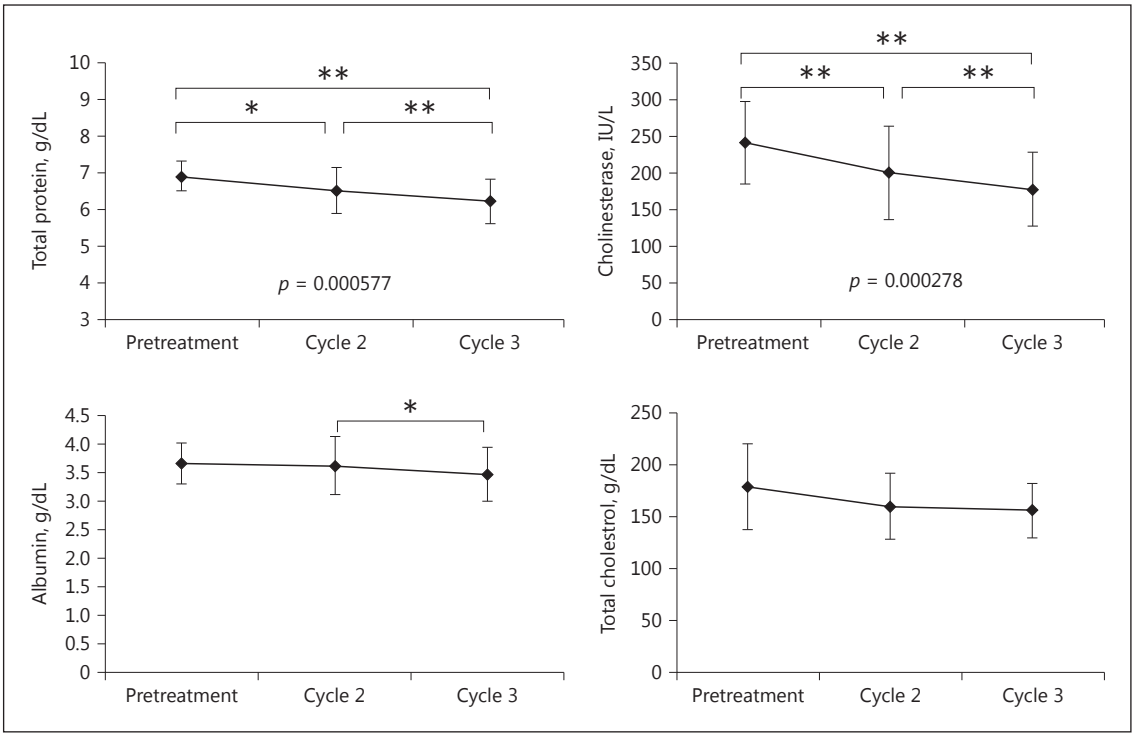

Fig. 2. Changes in nutritional status. * $p < 0.05$; ** $p < 0.01$.

Nutritional Status

The mean serum level of TP and cholinesterase was significantly decreased from 6.9 g/dL and 241.4 IU/L to 6.23 g/dL and 178.1 IU/L, respectively ($p = 0.000577$ and $p = 0.00278$). The mean serum level of Alb and total cholesterol was decreased from 3.7 g/dL and 167.9 IU/L to 3.53 g/dL and 157.3 IU/L respectively. However, there was no significant difference between them (Fig. 2).

Body Measurements by a Body Water Analyzer

The mean value of the body mass index and body fat percentage was significantly decreased from 21.9 kg/m^2 and 25.0% to 21.1 kg/m^2 and 22.7% respectively. The mean value of skeletal muscle mass and visceral fat area percentage was not changed (Fig. 3).

Discussion

It has been reported that the concentration of carnitine after chemotherapy is decreased after chemotherapy, especially using platinum-based anticancer drugs. Impaired expression of organic cation transporter novel 2, the principle carnitine transporter, in proximal tubular cells suppresses the reabsorption of carnitine and the urinary loss of carnitine was increased [7]. Ikezaki et al. [8] reported that the concentration of urinary carnitine levels differed significantly on days 2 and 3 after chemotherapy and were associated with self-reported fatigue. Conversely, Gomi et al. [9] reported that the change in plasma and urinary carnitine levels was not related to clinical factors.

These reports were based on the result of measurements of serum carnitine levels for one cycle of chemotherapy. The level of carnitine decreased below the low normal range after 2 cycles of treatment. Four patients were administered l-carnitine as soon as the results were known; however, time differences existed in the results obtained because the examination was performed by an outside institution. The chemotherapy for all of them was continued by administering l-carnitine.

Interestingly, the serum levels of TP, Alb, and ChoE had decreased significantly and appeared to be synchronized with the level of carnitine. It was thought that the adverse effects such as appetite loss and/or nausea caused by chemotherapy led to the deterioration of the nutritional status.

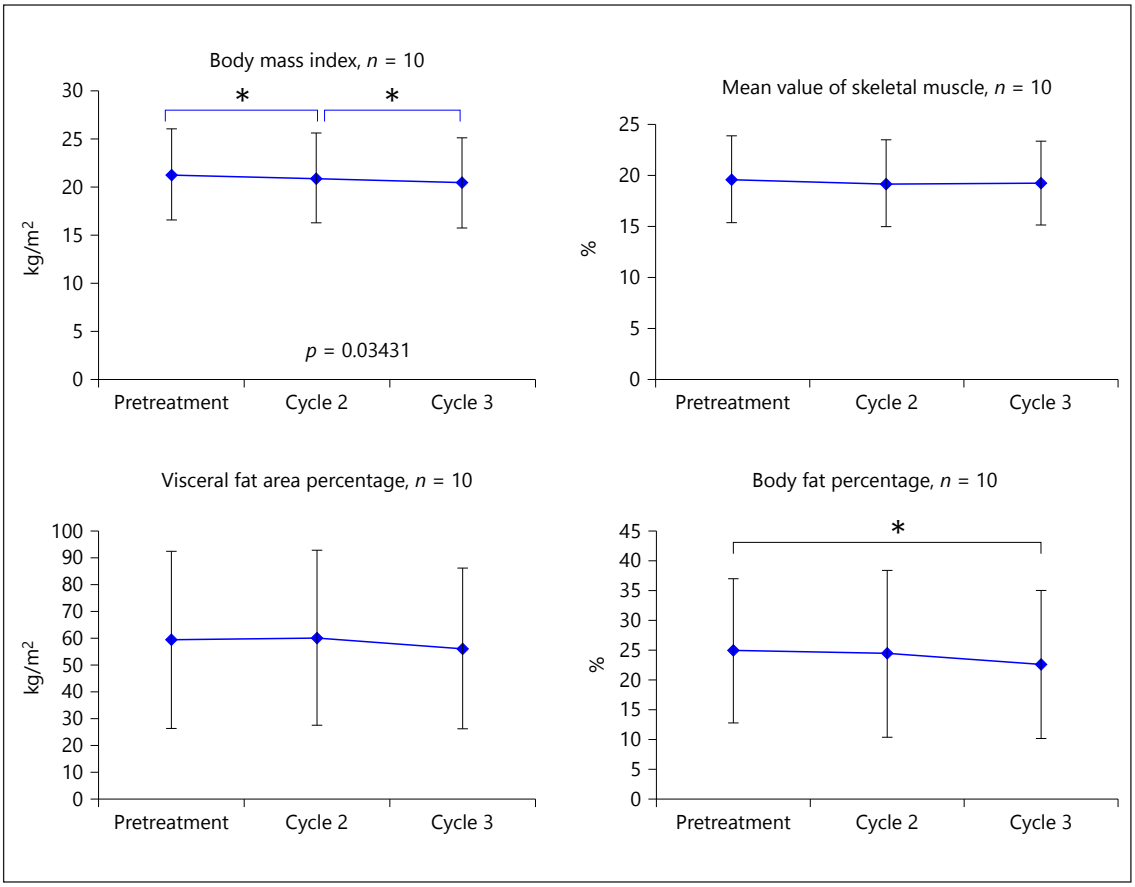

Fig. 3. Changes in body measurements. * $p < 0.05$.

Second, decreasing the serum level of carnitine might cause a deterioration in the serum Alb. It was reported that plasma carnitine levels correlated positively with serum Alb in patients on prolonged total parenteral nutrition [10]. Furthermore, there were many reports that supplementation of carnitine improved the nutritional status in hepatocellular carcinoma patients [11, 12] and hemodialysis patients [13]. Muto et al. [14] reported that carnitine deficiency inhibits fatty acid mobilization and oxidation for energy in skeletal muscles. Skeletal muscles are presumed to utilize branched-chain amino acids as a substitute for fatty acids to produce energy in liver cirrhosis patients. The decrease in Alb levels might be caused by this mechanism.

In our study, mean values of body mass index and body fat percentages were significantly decreased. However, the mean value of skeletal muscle mass and visceral fat area was not changed. That might be due to the short observation period at 2 cycles (6 weeks).

Three patients whose carnitine levels were below the low normal range were administered l-cartine and continued chemotherapy, while this regimen was discontinued in one patient. Five patients completed more than 4 cycles of chemotherapy.

These data suggest that the supplementation of carnitine for platinum-based chemotherapy might be effective in order to complete the chemotherapy regimen and to improve the quality of life of patients. We are planning the next trial if the supplementation of carnitine might indeed improve nutritional status and quality of life.

This study did have several limitations. This study was conducted at a single institute and the number of patients enrolled was small. Also, this study did not prove the relationship of the mechanism between carnitine levels and Alb.

In conclusion, carnitine levels might decrease in response to chemotherapy and some patients might need supplemental carnitine during such repeated chemotherapy regimens.

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This manuscript has not been published elsewhere and it has not been submitted simultaneously for publication elsewhere.

Disclosure Statement

The authors have no conflicts of interest to declare.

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