Induction Chemotherapy for Head and Neck Cancer Occur Potentially Free Carnitine Decrease

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Research Article

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Abstract

Background: Carnitine is related to malaise. Cisplatin is a cause of decreased carnitine. The purpose of this study was to elucidate the effects of one course of induction chemotherapy (IC) for head and neck cancer on blood carnitine levels, focusing on FC.

Methods: This single-center prospective study investigated 20 patients diagnosed with primary head and neck cancer who underwent IC with cisplatin, docetaxel, and 5-fluorouracil. FC, acylcarnitine (AC), and total carnitine (TC) levels were measured before starting therapy and on Days 7 and 21 after starting IC. In addition, malaise was evaluated before and after therapy using a visual analog scale (VAS).

Results: All subjects were men and the most common primary cancer site was the hypopharynx (9 patients). FC levels before starting therapy and on Days 7 and 21 were 47.7±2.2 μM/mL, 56.7±2.2 μM/mL, and 41.1±1.9 μM/mL, respectively. Compared with before the start of therapy, FC had significantly decreased on Day 21 (p=0.007). AC levels before starting therapy and on Days 7 and 21 were 12.5±1.2 μM/mL, 13.6±1.4 μM/mL, and 10.7±0.7 μM/mL, respectively. TC levels before starting therapy and on Days 7 and 21 were 60.2±2.5 μM/mL, 70.2±3.3 μM/mL, and 51.7±2.3 μM/mL, respectively. No significant differences in AC, TC or VAS were seen before the start of therapy and on Day 21.

Conclusions: After IC, a latent decrease in FC occurred without any absolute deficiency or subjective malaise. When concurrent chemoradiotherapy is planned following IC, supportive therapy with carnitine supplementation may be appropriate.

Introduction

Carnitine is a metabolic substance involved in fat metabolism. As can be seen from the definition of absolute deficiency as free carnitine (FC) < 36 μM/mL in the Guidelines for Diagnosis and Treatment of Carnitine Deficiency 2018,[1)] the blood kinetics of FC level are important. Cisplatin is a key drug in head and neck cancer treatments and is used in a variety of cases, such as induction chemotherapy (IC) and concurrent chemoradiotherapy (CCRT). However, cisplatin has an inhibitory action on organic cation/carnitine transporter 2 (OCTN2), and is known to cause a decrease in carnitine. Carnitine deficiency in turn leads to malaise, which is a common reason for the discontinuation of cancer therapy.[2)] Elucidation of how IC affects blood carnitine kinetics thus has important implications. However, no reports to date have examined associations between IC for head and neck cancer and changes in blood carnitine levels. The purpose of this study was to elucidate the effects of one course of IC for head and neck cancer on blood carnitine levels, focusing on FC.

Materials And Methods

Patients and ethics

Subjects were 20 patients ≥20 but <75 years old with stage III or IV-A head and neck cancer who underwent IC as the first treatment. Eastern Cooperative Oncology Group performance status (PS) was 0–2. Exclusion criteria were: administration of levocarnitine within the past month or current prescription of levocarnitine; pregnant or breastfeeding state, or possible pregnancy for women; or being considered as unsuitable for the trial by the patient's primary care physician. The enrollment period was from August 2, 2016 to December 31, 2019. Written consent for the trial was obtained from all patients prior to enrolment. This single-center, prospective observational study was approved (approval no. 2016-058) by the Research Ethics Committee of Tokyo Medical University Hospital.

Assessments

The primary endpoint was serum carnitine level before and after IC. Total carnitine (TC) and FC were measured from collected blood. As direct measurement of acylcarnitine (AC) was difficult, AC level was calculated as "TC − FC" based on the notion that "TC = FC + AC." Serum carnitine was measured before IC (Pre-IC), 7 days after starting IC (Post IC-7), and 21 days after starting IC (Post IC-21). In accordance with the Guidelines for Diagnosis and Treatment of Carnitine Deficiency 2018,[1)] FC <36 μM/mL was taken as absolute deficiency and AC/FC <0.4 as relative deficiency. The secondary endpoint was subjective malaise assessed at Pre-IC, Post IC-7, and Post IC-21 using a visual analog scale (VAS). The VAS had a total length of 70 mm and was scored in 1-mm increments, with 0 mm indicating no malaise and 70 mm indicating severe malaise. Staging was performed according to the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumors, 7th edition. Computed tomography (CT) was performed between 21 and 28 days after starting IC, and therapeutic effects were evaluated by a radiological specialist according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines.

Chemotherapy regimen

For IC, cisplatin and docetaxel were intravenously infused at a dose of 60 mg/m^2 each on day 1 and 5-fluorouracil was intravenously infused at a dose of 600 mg/m^2 on days 1–5 for 24 h.

Statistical analysis

Tests of normality were performed for concentrations of FC, AC, and TC levels, and for VAS score. When a normal distribution was identified, comparisons were made using a repeated-measures analysis of variance. Data that did not follow a normal distribution were tested with the Friedman test. Items showing a significant difference were tested with the Bonferroni method. Statistical analysis was performed using IBM® SPSS® Statistics 26 (IBM Corp., Tokyo, Japan). All tests were two-sided, with values of $p<0.05$ taken to indicate a significant difference.

Results

Patient characteristics

Patient characteristics are shown in Table 1. All patients were men, with a median age of 64 years (range, 48–73 years). The primary site was the oropharynx in 8 patients, hypopharynx in 9 patients, larynx in 2 patients, and maxillary sinus in 1 patient. The stage was Stage III in 4 patients and Stage IV in 16 patients. The therapeutic effect was complete response (CR) in 1 patient, partial response (PR) in 14 patients, stable disease (SD) in 4 patient, and progressive disease (PD) in 1 patients.

Changes in carnitine (FC, AC, and TC)

Changes in carnitine are shown in Figure 1. FC levels at Pre-IC, Post IC-7, and Post IC-21 were 47.7±2.2 μM/mL, 56.7±2.2 μM/mL, and 41.1±1.9 μM/mL, respectively. The level at Post IC-21 was significantly lower than at Pre-IC (P=0.007). The level at Post IC-7 was significantly higher than at Pre-IC (p=0.001). The level at Post IC-21 was significantly lower than at Post IC-7 (p=0.0001). Absolute deficiency (FC <36 μM/mL) was identified in 3 patients (15%) at Pre-IC, 1 patient (5%) at Post IC-7, and 1 patient (5%) at Post IC-21.

AC levels at Pre-IC, Post IC-7, and Post IC-21 were 12.5±1.2 μM/mL, 13.6±1.4 μM/mL, and 10.7±0.7 μM/mL, respectively. No significant differences were seen between any time points.

TC levels at Pre-IC, Post IC-7, and Post IC-21 were 60.2±2.5 μM/mL, 70.2±3.3 μM/mL, and 51.7±2.3 μM/mL at Pre-IC, Post IC-7, and Post IC-21, respectively. Levels tended to be lower at Pre-IC and Post IC-21, but no significant differences were seen (p=0.09). No significant difference was seen between Pre-IC and Post IC-7 (p=0.48). In contrast, TC was significantly lower at Post IC-21 than at Post IC-7 (p=0.01).

Changes in AC/FC

Changes in AC/FC ratio are shown in Figure 2. Ratios at Pre-IC, Post IC-7, and Post IC-21 were 0.28±0.04, 0.24±0.02, and 0.26±0.02, respectively. No significant differences were seen between any time points. Relative carnitine deficiency (AC/FC <0.4) was seen in 3 patients (15%) at Pre-IC and 4 patients (20%) at Post IC-21. No patients showed relative carnitine deficiency at Post IC-7.

Changes in VAS

Changes in VAS score are shown in Figure 3. No significant difference was seen between Pre-IC and Post IC-21 (p=0.949). VAS score was significantly higher at Post IC-7 than at Pre-IC (p=0.000232), and significantly lower at Post IC-21 than at Post IC-7 (p=0.000467).

Discussion

This study investigated changes in blood carnitine levels, including FC, in patients who underwent IC for head and neck cancer. FC levels were significantly lower at Post IC-21 than at Pre-IC. If 2 to 3 courses of IC were to be performed, FC levels would presumably be even lower. At the same time, absolute carnitine deficiency was seen in 1 patient (5%) and relative carnitine deficiency was seen in 4 patients (20%) at Post IC-21. Although FC was significantly decreased compared with before the start of therapy, few

patients reached absolute or relative carnitine deficiency. Therefore, the VAS score in this study also returned to nearly Pre-IC levels by Post IC-21. This is probably one reason why attention has not been focused on blood carnitine kinetics during IC. After IC, however, CCRT or surgery may be performed with the aim of achieving complete cure, and carnitine deficiency is known to occur with CCRT for head and neck cancer.[3] Globally, 3 courses of 100 mg/m^2 cisplatin are standard in chemoradiotherapy for head and neck cancer. If CCRT is performed in combination with 3 courses of cisplatin with the goal of complete cure when FC is significantly decreased from the Pre-IC level, development of absolute carnitine deficiency is not difficult to imagine. This could lead to exacerbation of malaise and difficulty in continuing treatment. Longer duration of radiotherapy leads to worsened prognosis.[4] As FC can be supplemented with food and also with L-carnitine preparations, CCRT planned for after IC may need to begin after some form of FC supplementation has been administered.

Of the carnitine in the body, 75% is consumed orally. The rest is biosynthesized in the cardiac muscle, kidneys, and brain.[15–17] The main causes of carnitine deficiency are thus insufficient dietary intake and decreased muscle mass. Muscle mass is known to decrease in cancer patients. Head and neck cancer patients show a tendency for an unbalanced diet accompanied by high alcohol consumption and dysphagia due to pharyngeal tumors. Against this background, malnutrition from decreased dietary intake is seen in 25–50% of patients.[5–7] Despite advances in supportive therapy, dietary intake falls even further when cisplatin is used due to nausea and other adverse effects.[8] In the energy metabolism of cancer cells, a change occurs from aerobic metabolism of fatty acids to anaerobic metabolism with glycolysis. This is called the Warburg effect, in which AC is increased and FC is decreased due to incomplete β oxidation, increasing the AC/FC ratio.[9] Among our patients, absolute carnitine deficiency was seen in 3 patients (15%) and relative carnitine deficiency in 3 patients (15%) before the start of IC. Thus, carnitine deficiency appears to occur easily in head and neck cancer patients both before and during treatment.

The distribution of carnitine is related to OCTN, ATB$^{0,+}$, OAT9, and other proteins. OCTN2 is involved mainly in carnitine transport.[10] This sodium-dependent carnitine transporter is seen in nearly all tissues in the body.[11–14] Almost all carnitine is filtered into the urine via the renal glomeruli, then reabsorbed into the body by OCTN2 expressed in the renal tubules.[15–17] Cisplatin blocks OCTN2 and inhibits the expression of OCTN2 distributed in tubular cells due to nephrotoxicity.[18] Cisplatin is thus an anticancer agent that increases the urinary excretion of carnitine and reduces the expression of OCTN2, causing carnitine deficiency. In our patients, elevated blood carnitine levels were seen on Post IC-7. Blood carnitine levels are reportedly temporarily elevated with the administration of anticancer agents.[19–21] Unfortunately, the physiological reasons for this have yet to be clarified. One possibility has been suggested in the literature that migration of FC into cells is blocked and blood FC is temporarily elevated when anticancer agents block the OCTN2 expressed on cell membranes.[22] Despite the significant elevation of FC on Post IC-7 in our patients, malaise worsened on the VAS. This is thought to be because FC in blood is not efficiently used in energy production, supporting the hypothesis that FC migration into

cells is blocked when anticancer agents block OCTN2. Physiological elucidation of carnitine blood kinetics is awaited.

In this study, a significant decrease in FC was shown after one course of IC. That is, 1 course of IC achieved a latent decrease in FC, even though no absolute carnitine deficiency developed and the VAS score had also improved to the same as Pre-IC. CCRT or surgery was performed after IC as radical treatment. These therapies require supportive treatments to be performed in the best possible general condition. In the future, we will investigate whether any difference in malaise, treatment completion rate or other parameters for CCRT are apparent between groups with and without FC supplementation after IC. If substantial results are achieved, this could lead to the establishment of new supportive therapies.

Conclusion

The effects of IC for head and neck cancer on blood carnitine kinetics, including FC, were investigated. FC was significantly decreased at Post IC-21 compared with Pre-IC. After IC, FC was in a state of latent decrease. This suggests that with supportive therapy based on carnitine supplementation, CCRT or other therapy following IC can be started with the patient in better condition.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research. This study was approved (approval no. 2016-058) by the Research Ethics Committee of Tokyo Medical University Hospital. informed consent was obtained from all patients or, if patients are under 18, from a parent and/or legal guardian.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not Applicable

Authors' contributions

TI, KT and HS developed the study concept. TI were responsible for data management and statistical analysis. TI, KY and HS reviewed the clinical background of the results. TI and KY wrote the draft of the report. All authors critically reviewed and revised the manuscript.

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Authors' information (optional)

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Tables

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

Figures

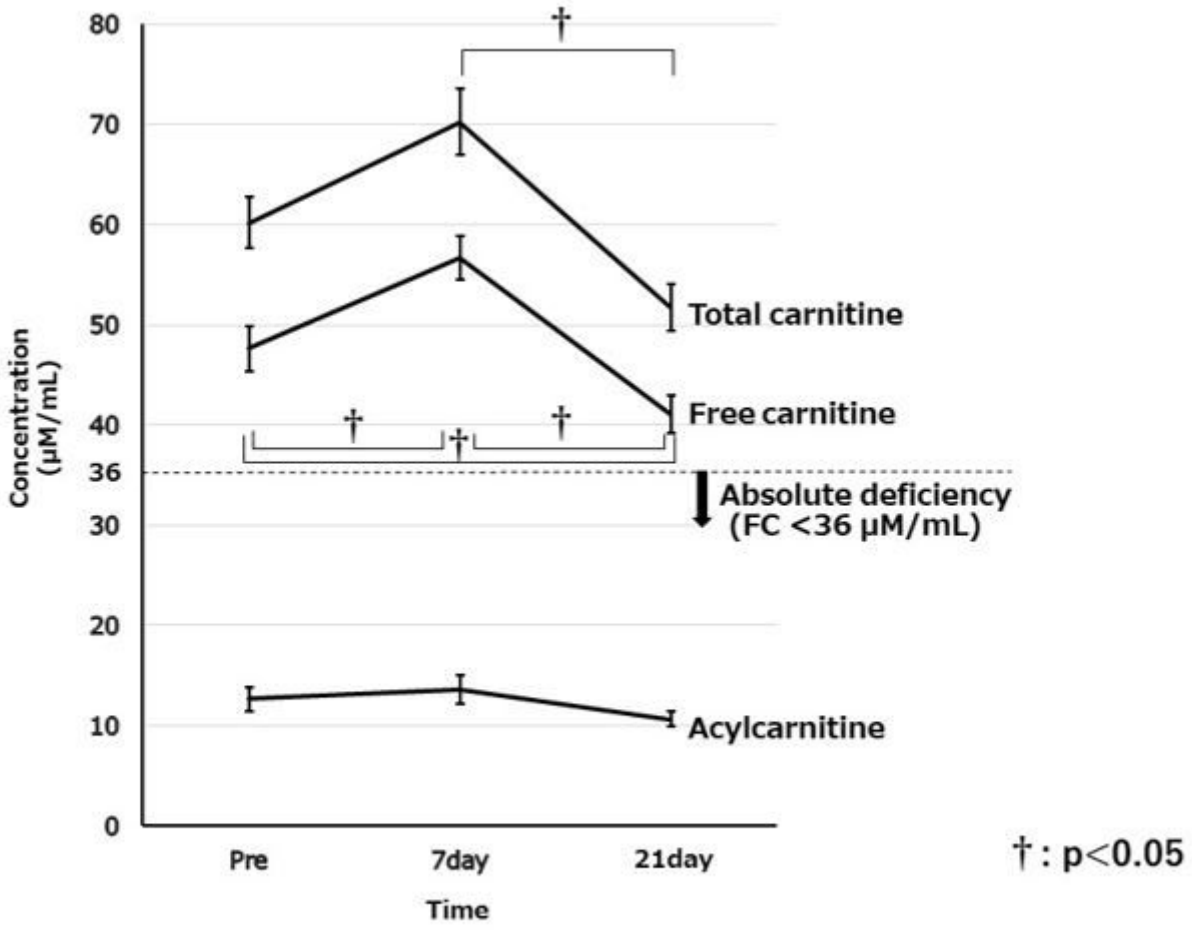

Figure 1

Changes in carnitine values

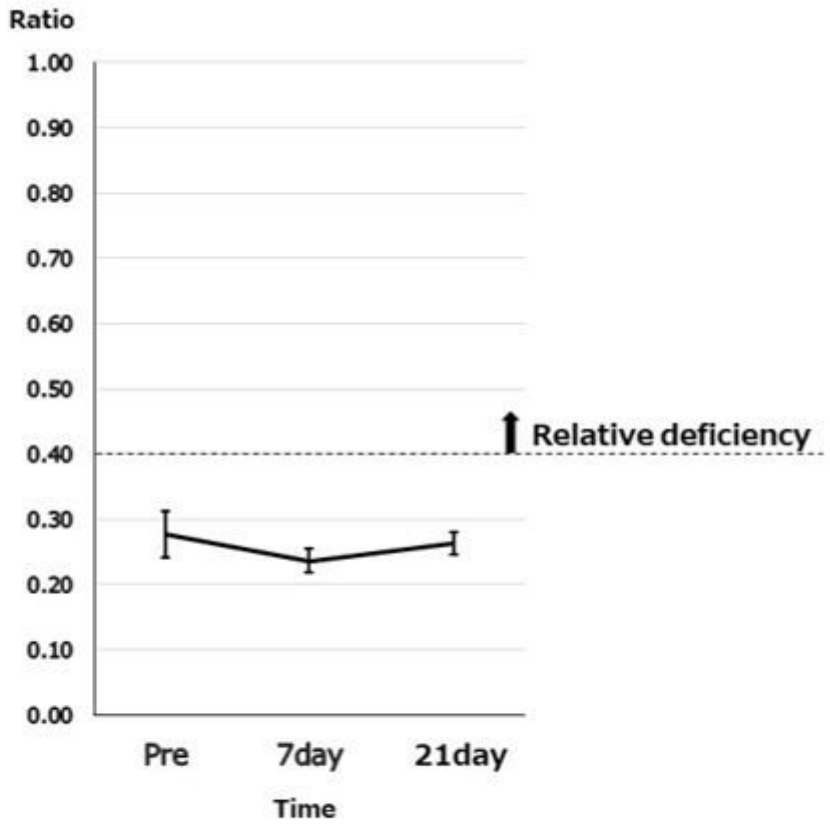

Figure 2

Changes in acylcarnitine/free carnitine ratio

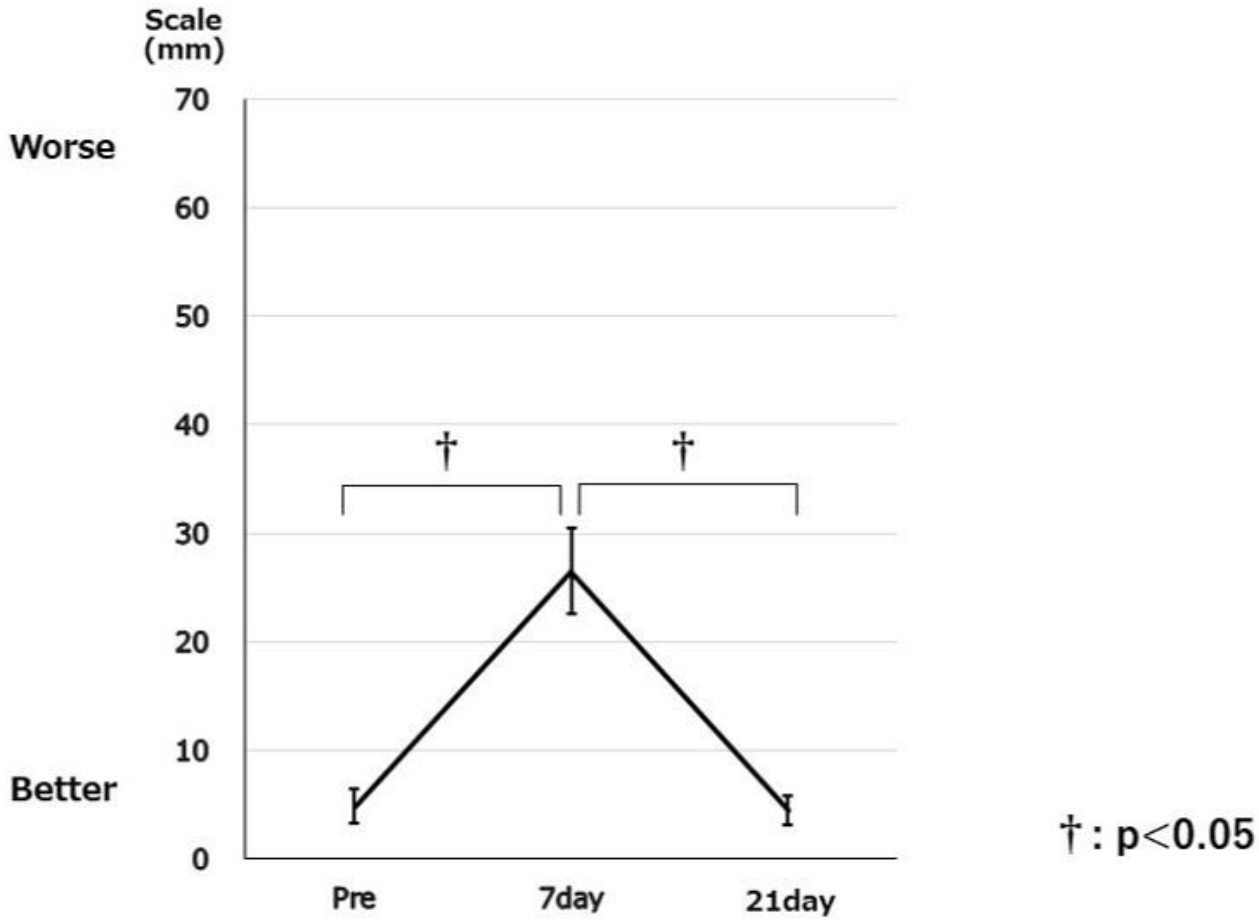

Figure 3

Changes in visual analog scale

Supplementary Files

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- Table1.jpg