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ORIGINAL ARTICLE

Can levocarnitine supplementation improve fatigue caused by sunitinib as a treatment for renal cell carcinoma? A single-center prospective pilot study

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Abstract

Purpose To evaluate the potential role of levocarnitine supplementation for cancer-related fatigue in patients treated with sunitinib.

Methods Patients treated with sunitinib for unresectable or metastatic renal cell carcinoma were enrolled prospectively. Assessment of fatigue in each patient was done using the Brief Fatigue Inventory (BFI) questionnaire. Evaluation of fatigue and the serum carnitine level was done at baseline, 2 weeks, and 4 weeks after sunitinib therapy was initiated. All patients were treated with sunitinib 37.5 mg or 50 mg/day orally, with a 4-week administration and 2-week discontinuation schedule.

Results Ten patients were finally enrolled in the study. Seven of them had worsened fatigue at the 2-week assessment and levocarnitine was administrated. All these seven patients whose serum carnitine level at 2 weeks was worse than at the baseline improved after 2-week-L-carnitine supplementation. For six of the seven (85.7%) patients who had L-carnitine supplementation, the BFI score at 4 weeks decreased compared to that at 2 weeks, which indicated improvement of fatigue.

Conclusions Levocarnitine supplementation for cancer-related fatigue in patients treated with sunitinib appears to have a potential benefit. However, further study with a larger number of patients and longer follow-up is crucial to confirm this.

Keywords Cancer-related fatigue · Renal cell carcinoma · Sunitinib · Carnitine

Introduction

Sunitinib is a tyrosine kinase inhibitor used for treatment of metastatic renal cell carcinoma. Because its survival benefit is superior to interferon-alpha therapy [1], sunitinib is widely used. However, molecular targeted agents such as sunitinib have various adverse effects that often greatly impact the patient's quality of life [2–4]. It is crucial for clinicians to manage these side effects and continue the therapy and achieve a long treatment duration that may lead to improvement of the patient's survival period.

Patients with cancer report that they frequently experience general malaise and fatigue before and after treatment, which is known as cancer-related fatigue (CRF). It is mandatory for clinicians to evaluate the degree of their fatigue and manage the symptoms. Non-pharmacological approaches such as exercise, yoga, meditation, and nutrition management are recommended as options to relieve CRF [5–7]. Multifactorial mechanisms are reported to be involved in CRF [8, 9] and no specific pharmacological approach is as yet established to treat it.

Levocarnitine (L-carnitine) is an amino acid that is naturally synthesized in the human body and provided by daily intake. Because it is involved in energy metabolism, the role of L-carnitine in CRF had been investigated [10, 11]. CRF induced by anticancer drugs such as cisplatin is reported and the possible improvement of CRF by carnitine supplementation has also been reported [12]. Although fatigue in patients treated with sunitinib is well known [2, 3], the mechanism and specific pharmacological approach to deal with the symptoms has not been investigated. Thus, we aimed to explore the role of L-carnitine for CRF in patients with unresectable or

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metastatic renal cell carcinoma treated with sunitinib in the present pilot study.

Patients and methods

A prospective single-center study was designed (Fig. 1). All data were obtained after approval of our institutional review board (No. 262-96). The study period was from November 2014 through May 2017. Clinical data were obtained from medical records. The criterion for L-carnitine administration was a worse fatigue score after 2-week sunitinib treatment compared to the baseline score. Patients who were going to receive sunitinib therapy for metastatic or unresectable renal cell carcinoma were included. No patients who had a history of previous molecular-targeted agent treatment were included. Written informed consent was obtained from all patients in our study. Patients with impaired ECOG performance status (PS 3 and 4) were also excluded from the study. The initial dose of sunitinib (37.5 mg or 50 mg per day) was decided by the clinician in charge. The treatment schedule for sunitinib was 4 weeks of medication and 2 weeks of discontinuation as a single course. Treatment discontinuation due to adverse events such as a platelet decrease or hand-foot syndrome was decided when symptoms of grade 3 or more (CTCAE ver.3.0) appeared. Patients reporting fatigue by questionnaire after 2 weeks of sunitinib therapy were administrated L-carnitine 1500 mg per day orally. Those who did not report worse fatigue compared to the baseline did not have any supplementation.

To compare continuous variables, the Mann-Whitney *U* test was used. A p value of less than 0.05 was considered to indicate statistical significance. All data were analyzed using EZR ver.1.35 (Saitama Medical Center, Jichi Medical University [13]. The Brief Fatigue Inventory (BFI) [14, 15] questionnaire was used in our study. A higher score indicates more severe fatigue in the BFI. All patients were evaluated using these questionnaires at baseline (pre-sunitinib), after 2 weeks of sunitinib therapy, and at 4 weeks, which was the end of the first course of sunitinib medication. Changes in the score of the BFI questionnaire between the baseline and 2 weeks and 4 weeks were evaluated for each patient. The total serum carnitine level in each patient was evaluated simultaneously with BFI evaluation by BML (BML Inc., Tokyo, Japan) using an enzymatic cycling method. Changes in the serum carnitine level between the baseline and 2 weeks and 4 weeks were also evaluated for each patient. Measurements were done at exactly 2 and 4 weeks. However, within 1 week prior to sunitinib administration was accepted as the baseline measurement window.

Results

Ten patients were enrolled in the study. Total carnitine level of all ten patients at each point was shown (Supplementary Fig. 1).

The patients' backgrounds are listed in Table 1. In the fatigue assessment at 2 weeks after the initiation of sunitinb therapy, seven of the ten (70%) patients had worse BFI scores than at the baseline and received L-carnitine medication for 2 weeks. The other three did not receive L-carnitine supplementation.

The total serum carnitine level changes from the baseline and each evaluation point are shown in Fig. 2a. Patient numbers (Pt Nos.) 1 to 7 were the ones who had L-carnitine supplementation from 2 weeks. All seven patients whose serum carnitine level at 2 weeks was worse than at the baseline improved after 2 week L-carnitine supplementation (Fig. 2a). The BFI score changes compared to the baseline and each evaluation point are shown in Fig. 2b. For six of the seven (85.7%) patients who had L-carnitine supplementation, the BFI score at 4 weeks decreased compared to that at 2 weeks, which indicated improvement of fatigue. In patient numbers 3, 5, and 7, who were representative cases of improvement of fatigue by carnitine supplementation in this series, administration of L-carnitine increased the serum carnitine level, and the BFI score improved compared to 2 weeks (Fig. 3a, b).

The differences in the BFI between the baseline and 2 weeks according to initial sunitinib dose are shown in Fig. 4. Patients treated with 50 mg daily of sunitinib had worse BFI scores than those receiving 37.5 mg daily (Mann-Whitney *U* test, $p = 0.0319$). There was no additional supplementation in the study period for the ten patients in the study.

Discussion

Sunitinib is a tyrosine kinase inhibitor widely used for renal cell carcinoma. Although the oncological effect is expectable, adverse effects such as fatigue often emerge. One of the reasons for the fatigue due to sunitinib is hypothyroidism, especially when using it for a longer period. However, even soon after sunitinib administration, i.e., within 2 weeks, fatigue may occur and the mechanism is not known. A global phase 3 trial showed that approximately half of patients had fatigue regardless of the grade [16]. A Japanese phase 2 study also showed that 69% of patients who received sunitinib treatment for metastatic renal cell carcinoma experienced fatigue [17]. Compared to pazopanib, which is a tyrosine kinase inhibitor for renal cell carcinoma, sunitinib induces more fatigue as assessed by the FACIT-F questionnaire [18].

Carnitine is a vitamin-like substance that is necessary for the transportation of acyl-CoA across the inner mitochondrial membrane and helps energy production via beta-oxidation

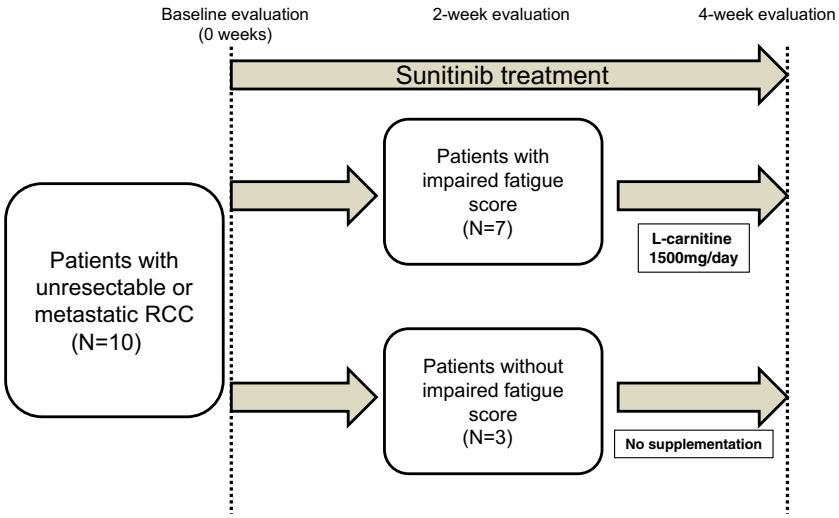

Fig. 1 Schematic design and patients included in the study

[19]. Daily intake delivery and synthesis in the human body produce carnitine, and organic cation transporter novel 2 (OCTN2) plays an important role in the reabsorption of carnitine at the renal glomerulus [20]. The beneficial role of carnitine in CRF is controversial. A multicenter, placebo-controlled, randomized, double-blind trial for advanced pancreas cancer concluded that supplementation with carnitine improved the patients' nutritional status, quality of life, and overall survival [11]. Conversely, a double-blind, placebo-controlled study of L-carnitine for CRF including a large number of patients having invasive malignancies reported a negative result for fatigue improvement assessed by the BFI. In that study, supplementation with 2 g of L-carnitine for 4 weeks failed to achieve improvement of fatigue [21]. According to these randomized studies, the benefit of L-carnitine supplementation for CRF caused by an advanced cancer burden itself is not clear.

Table 1 Clinical characteristics of patients

	$N = 10$
Age at median (range)	70.5 (45–79)
Histology	
Clear cell carcinoma	9 (90%)
Papillary cell carcinoma	1 (10%)
Clinical T stage	
T1a	2 (20%)
T1b	4 (40%)
T2	2 (20%)
T3b	2 (20%)
Metastatic site	
Lung	4
Pancreas	4
Lymph node	2
Liver	2
Bone	3
Treatment line	
1st	9 (90%)
2nd	1 (10%)
Initial treatment dose of sunitinib (mg/day)	
37.5	4 (40%)
50	6 (60%)
Sunitinib course at evaluation in the study	
1st	10 (100%)

For CRF caused by therapeutic agents, L-carnitine was reported to be beneficial in a previous study. Supplementation for patients receiving treatment with cisplatin is reported to have a positive effect on fatigue induced by chemotherapy. One-week supplementation with L-carnitine improved fatigue assessed by the FACT-F questionnaire in patients who received cisplatin-based or ifosfamide-based chemotherapy for nonanemic cancers [12]. Cisplatin is known to inhibit the expression and functions of OCTN2 in vitro. Carnitine uptake by HEK293 cells, which overexpress human OCTN2, revealed that cisplatin inhibits uptake of carnitine [20]. Interestingly, sunitinib also strongly inhibits the uptake of carnitine [20]. These findings are of clinical interest with regard to the beneficial role of carnitine supplementation for fatigue in renal cell carcinoma patients treated with sunitinib. Moreover, levocarnitine is known for its potential role in modulating the inflammatory response in cancer cachexia, especially in pancreatic cancer patients [22].

In the present study, seven of ten (70%) patients had decreased serum carnitine levels after a 2-week sunitinib treatment. However, the serum carnitine levels were restored by supplementation in all seven of them. Six of these seven had improved BFI scores at the 4-week evaluation compared to the 2-week evaluation. Although this was a pilot study with a small number of patients, the results may indicate the potential role of carnitine supplementation for fatigue induced by

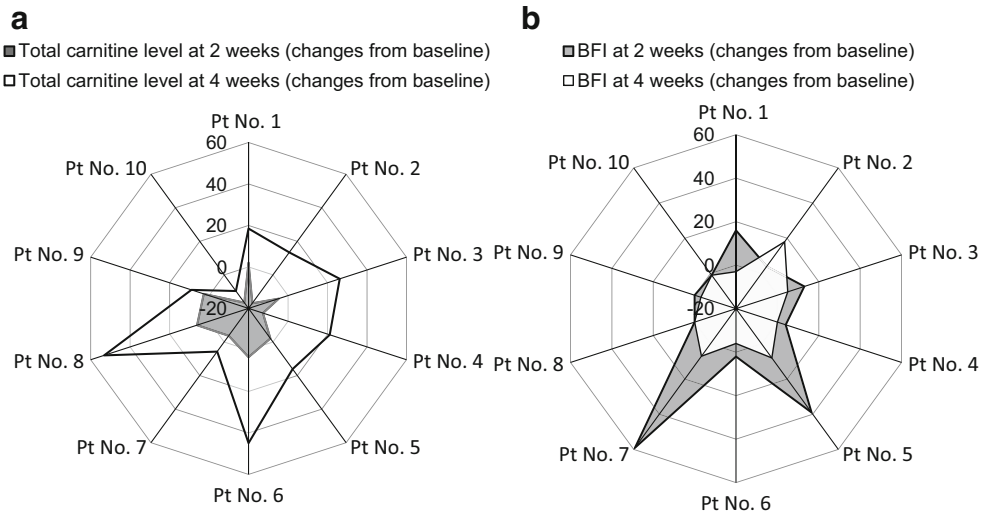

Fig. 2 Changes in total serum carnitine levels (**a**) and BFI scores (**b**) in study period. Patients 1 to 7 had L-carnitine supplementation

sunitinib. Three representative patients (patient numbers 3, 5, and 7) had their fatigue relieved to a great extent after administration of carnitine. However, there was no dramatic change in the fatigue status of the other patients who had supplementation.

In our cohort, we especially focused on three patients (patient numbers 3, 5, and 7) because of their improvement of fatigue (BFI score) and serum carnitine level. Fatigue improved after 2 weeks of carnitine supplementation (Fig. 3). However, the increasing level of serum carnitine and improving degree of BFI score did not correlated. For example, Pt No. 3 had best recovery of serum carnitine level after 2 weeks of supplementation. However, improvement of fatigue according to BFI score was minimum among these three patients. On the other hand, Pt No. 7 had great improvement of fatigue and activity in daily life although the degree of change in serum carnitine level was not so remarkable. Therefore, the impact of serum carnitine level on fatigue may differ among individuals.

Underlying multifactorial causes of CRF may explain the different responses among the patients. Cytokines such as interleukin-6, interleukin-1RA, transforming growth factor (TGF)-β, and soluble tumor necrosis factor receptor 2 (sTNF-R2) are also reported to be associated with CRF in patients receiving chemotherapy [23, 24]. TGF-β expression in lymphocytes has a potential role as a biomarker for fatigue induced by adjuvant chemotherapy in breast cancer patients [23]. Because of the multifactorial causes of CRF, a single therapeutic supplementation approach such as the use of L-carnitine for patients having cancer may only benefit a limited population. Therefore, various approaches have to be considered for individual patients.

Recently, the sunitinib schedule is often modified into 2-week administration and 1-week discontinuation because it may help to maintain QOL and a long treatment duration in some patients [25]. Thus, the effect of the initial dose of sunitinib on fatigue at 2 weeks compared to the baseline was also evaluated. When assessing fatigue using the BFI, a significant difference was confirmed between the patients with the 37.5 mg initial dose and those with the 50 mg initial dose. Considering the results, a reduction of the initial dose may be a useful management strategy for patients who have fatigue soon after the induction of sunitinib treatment.

The main limitations of this study are the small number of patients and the short follow-up period. We only focused on the first 4 weeks after sunitinib treatment. Thus, impact of supplementation in a long term is unknown. Furthermore, in the present study, we did not use any placebo drugs in the non-

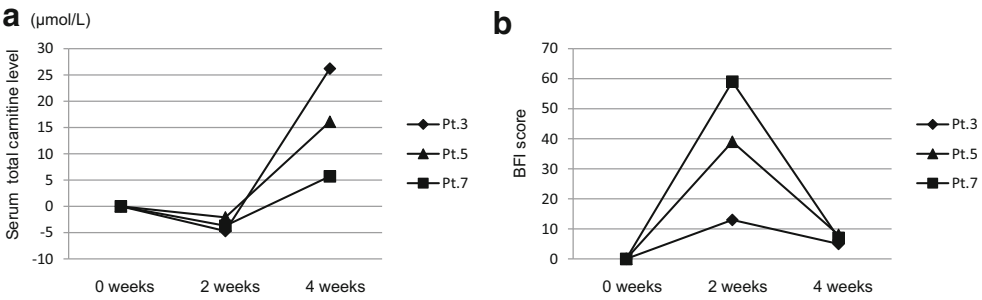

Fig. 3 Representative patients who had improvement of total serum carnitine level after supplementation (**a**) and BFI (**b**). Changes in total serum carnitine levels (**a**) and BFI scores (**b**) compared with the baseline of each patient, respectively

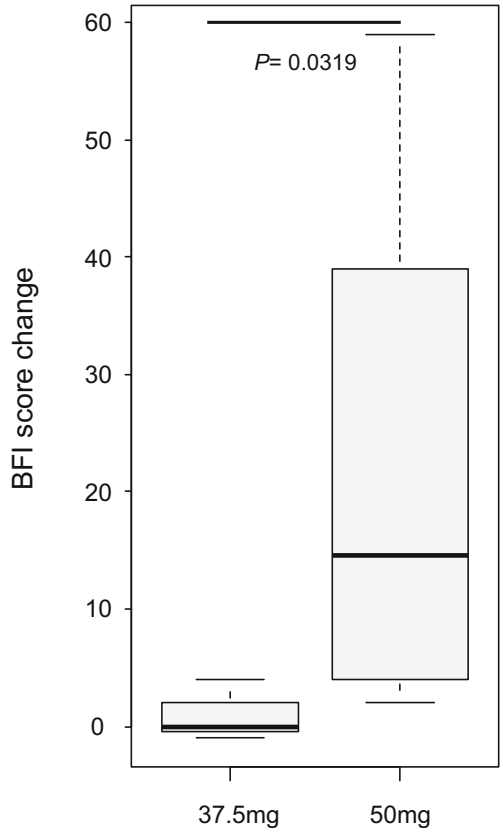

Fig. 4 Comparison of BFI changes from the baseline to 2 weeks of sunitinib therapy according to the initial sunitinib dose

supplement group. Therefore, we are not able to assess natural course of fatigue in metastatic RCC patients and we could not exclude the possibility of a placebo effect of the administration of L-carnitine. In addition, there is a possibility that fatigue improvement in some patients might have been due to the induction of the anticancer treatment itself. Moreover, supplementation dose of L-carnitine was only 1500 mg/day and there is no data of dose dependency. Since carnitine intake is mainly due to daily meal, we could not rule out the possibility that serum carnitine level was affected by the meal. Some patients had increased serum total carnitine level without supplementation. To further investigate the role of carnitine in this field, a prospective study including a larger number of patients with a randomized design is essential.

Conclusions

Fatigue in renal cell carcinoma patients treated with sunitinib may partly be due to a decrease of the serum carnitine level, and carnitine supplementation may have a potential role in improving fatigue. However, this was a pilot study with small number of patients, so a further study with a large number of patients is needed to confirm the results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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