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Cancer Cachexia May Hinder Pain Control When Using Fentanyl Patch

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The objective of this study was to evaluate the influence of cancer cachexia on pain control in cancer patients receiving a transdermal fentanyl patch (FP) and to investigate whether dry skin was a factor related to cancer cachexia and uncontrolled pain. We retrospectively reviewed the medical records of 77 patients receiving FP treatment for the first time, who were classified into cancer cachexia and non-cancer-cachexia groups, according to European Palliative Care Research Collaborative criteria. On day 7 after FP administration, the mean FP dose and morphine equivalent dose (MED) in the cancer cachexia group were significantly higher than in the non-cancer-cachexia group. Additionally, in the cancer cachexia group, there was a significantly larger degree of variation in pain intensity over 7 d than in the non-cachexia group. In patients who were switched from FP to morphine injection, the mean pain intensity and MED on day 3 after morphine injection were significantly lower than those immediately before morphine injection. Subsequently, to investigate whether dry skin was involved in poor pain control in the cancer cachexia group, transepidermal water loss (TEWL) was compared between 15 additional patients classified into cancer cachexia and non-cancer cachexia groups; the mean TEWL in the cancer cachexia group was found to be significantly lower. Our data suggest that cancer cachexia may be a risk factor for poor pain control in patients receiving FP treatment, and that uncontrolled pain in FP treatment may be caused by the inhibition of fentanyl transdermal absorption due to dry skin.

Key words transdermal fentanyl patch; cancer cachexia; dry skin; uncontrolled pain

INTRODUCTION

Fentanyl has a high lipid solubility and low molecular weight, which makes it suitable for transdermal administration.[1,2] Currently, the transdermal fentanyl patch (FP) has been used worldwide to relieve cancer pain, and is particularly useful for patients with dysphagia. Available FPs in Japan are Durotep® MT patch (Janssen Pharmaceutical K.K., Japan), Oneduro® patch (Janssen Pharmaceutical K.K.), and Fentos® tape (Hisamitsu Pharmaceutical Co., Inc., Japan). The FP should be replaced every 72 h (Durotep® MT patch) or 24 h (Oneduro® patch and Fentos® tape).

We previously reported that low body fat may decrease transdermal fentanyl absorption in cancer patients.[3] Additionally, we showed that there was a significant relationship between poor nutritional status and increased pain intensity in cancer patients receiving FP treatment.[4] These results imply that poor nutritional status may be a risk factor for poor pain management in cancer patients receiving FP treatment.

Most advanced cancer patients have cancer cachexia with anorexia, weight loss, decreased body fat and muscle, dehydration, and electrolyte abnormalities.[5,6] Heiskanen *et al.* assessed cancer cachexia using body mass index (BMI) as a single criterion and found that plasma levels of fentanyl in patients with cachexia (mean BMI, 16 kg/m^2) were significantly lower than in patients with no cachexia (mean BMI, 23 kg/m^2).[7] However, it is difficult to evaluate cancer cachexia with complicated metabolic disorders using only BMI. Moreover, no previous studies have examined the influence of cancer cachexia on pain control in cancer patients receiving FP treatment. Additionally, dry skin is a common physical sign in advanced cancer patients with cancer cachexia,[5] and no previous research has investigated whether dry skin is related to decreased plasma levels of fentanyl in cancer patients receiving FP treatment.

Recently, the European Palliative Care Research Collaborative (EPCRC) provided a definition and classification of cancer cachexia, which have obtained international consensus.[8] Evaluating cancer cachexia using the EPCRC criteria and investigating whether cancer cachexia influences pain control with FP treatment will generate useful information for healthcare professionals in palliative care.

In this study, in order to evaluate whether cancer cachexia influences pain control by FP, we retrospectively investigated the relationship between cancer cachexia and pain intensity during FP use and the variation in pain intensity when switching FP to morphine injection. Furthermore, we focused on dry skin as a factor causing poor pain management in cancer patients receiving FP treatment and compared skin dryness in patients with and without cancer cachexia.

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MATERIALS AND METHODS

Relationship between Cancer Cachexia and Pain Control with Transdermal FP

Patients

Participants were Japanese adults with cancer who were inpatients at Iwate Medical University Hospital between April 1, 2014 and December 31, 2016, who were undergoing initial treatment for chronic cancer-related pain with transdermal FP (Durotep® MT patch or Fentos® tape), and who were switched from oxycodone or morphine. We excluded patients with fever ($\geq$ 40°C); radiation treatment; cutaneous disease; those who had been prescribed medications that influenced pain intensity, such as anticancer drugs and analgesic adjuvants (except for non-steroidal anti-inflammatory drugs [NSAIDs]); those who were not switched from morphine or oxycodone to transdermal FP according to a package insert; and those who did not receive the increase in the transdermal FP dose properly (*e.g.*, patients who received rapid-acting opioids over three times a day or had over six points of pain intensity on a numeric rating scale [NRS]). This retrospective survey was reviewed and approved by the Iwate Medical University Ethics Committee (approval no. MH-2019-088).

Retrospective Survey

Data on sex, age, type of cancer, FP dose, type of FP, and dose of opioid prior to the use of FP, concomitant drugs, laboratory test results (including alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GTP), and serum creatinine (Scr)), and pain intensity (NRS: 11-point scale from 0 to 10) were retrospective surveyed using medical records or patients' compliance instruction records. Creatinine clearance (Ccr) was estimated using the Cockcroft–Gault equation. The evaluation of cancer cachexia was performed using patients' information at the onset of FP treatment according to EPCRC criteria. Patients who had more than 5% loss of stable body weight over the past 6 months, those who had a BMI of less than 20 kg/m^2 and ongoing weight loss of more than 2%, or those who had sarcopenia and ongoing weight loss of more than 2% were classified into the cancer cachexia group, while the remaining patients constituted the non-cancer-cachexia group.

Evaluation of Pain Intensity

The comparison of pain intensity between the cancer cachexia and non-cancer-cachexia groups was performed using pain intensity on day 7 after FP treatment, which was calculated as the mean of all measurements of pain intensity on that day for each patient. The comparison of the change in pain intensity between the groups was performed using the value derived by subtracting the minimum pain intensity measurement from the maximum measurement over 7 d after FP treatment.

Additionally, to evaluate the change in pain control when FP was switched to morphine injection in the cancer cachexia group, we compared pain intensity immediately before morphine injection treatment with pain intensity on day 3 after morphine injection treatment.

Evaluation of Morphine Equivalent Dose (MED)

To compare patients' opioid daily dose between the cancer cachexia and non-cancer-cachexia groups, and to compare cancer-cachexia patients' opioid daily dose before switching FP to morphine injection with that after switching, the MED for each patient was used. The MED was calculated by equating a morphine suppository of 20 mg, 20 mg of oral oxycodone (extended-release and rapid-acting), and a FP preparation of 12.5 μg/h with 30 g of oral morphine or a morphine injection of 15 mg. For the comparison of MED between the groups, the MED on day 7 after FP treatment in each group was used. For the comparison of cancer-cachexia patients' MED before switching FP to morphine injection with that after switching, we assessed MED immediately before the morphine injection treatment and on day 3 after the morphine injection treatment.

Evaluation of Cutaneous Dryness

Patients

Japanese adults with cancer who were inpatients at Iwate Medical University Hospital between June 1, 2017 and December 31, 2017, and who were receiving FP administration for the first time were included in this study. Each participant provided written informed consent. Additionally, the presence/absence of cancer cachexia was evaluated using information obtained at the start of FP treatment, according to the EPCRC criteria. This study protocol was reviewed and approved by the Iwate Medical University Ethics Committee (approval no. H29-31).

Evaluation of Cutaneous Dryness and Cancer Cachexia

To compare cutaneous dryness between the cancer cachexia and non-cancer-cachexia groups, transepidermal water loss (TEWL), an index of cutaneous dryness,[9] in each patient was measured using the measuring device Tewameter TM 300 (Courage + Khazaka, Cologne, Germany). The skin of patients was intact, with no lesions at the measurement sites (brachial region). Measurements were taken in a room at a temperature between 20 and 25°C, and with a relative humidity between 40 and 50%. The mean of three measurements was used in this comparison. Patients rested in the room for 10 to 20 min before the measurement for acclimatization. They were instructed not to use any products on the skin on the day of measurement (for at least 12 h) or perform any strenuous movement before the evaluation. All measurements were taken in the morning by the same examiner, previously trained on how to use the measuring device.

Statistical Analysis Laboratory data were compared between the groups using chi-squared, Student's *t*-test, and Mann–Whitney *U* test. The comparison of laboratory data between before and after switching from FP to morphine was performed using paired *t*-test and Wilcoxon signed-rank test. Differences were considered statistically significant if *p*-values were <0.05. Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, U.S.A.).

RESULTS

Patients in Retrospective Analysis A total of 106 patients were eligible for this study. From them, 6 patients discontinued the administration of FP within 7 d after the start of FP treatment, 15 had not provided necessary information for evaluating cancer cachexia or pain intensity, 3 had not been switched from morphine or oxycodone to FP according to the package insert, 1 had a fever (40°C), and 4 were taking medications that influenced pain intensity; these 29 patients were therefore excluded from the analysis. Finally, data from 77 patients were analyzed in this study.

Characteristics of Patients According to Group Of the 77 patients included in the analysis, 30 were classified into the

cancer cachexia group and the remaining 47 patients constituted the non-cancer-cachexia group.

At the time of commencing FP administration, gender ratio, age, FP dose, type of FP, ALT, AST, γ-GTP, Scr, Ccr, use of concomitant drugs, stage of cancer, and primary cancer location were not significantly different between the two groups (Table 1). Additionally, opioid use (oral oxycodone and morphine) and MED immediately before FP treatment were not significantly different between the two groups (Table 1).

On day 7 after FP administration, there were no significant differences in ALT, AST, γ-GTP, Scr, Ccr, or pain intensity between the two groups (Table 2). However, the mean FP dose and MED in the cancer cachexia group were significantly higher than those in the non-cancer-cachexia group (Table 2). Additionally, the mean change in pain intensity in the cancer cachexia group was significantly larger than that in the non-cancer-cachexia group (Fig. 1).

Patient Characteristics before and after Switching from FP to Morphine Injection Of 30 patients classified into the cancer cachexia group, 9 were switched from FP to morphine injection because of dysphasia or uncontrolled pain (Table 3). Their mean age was 56.8 ± 7.6 years. Concomitant drugs were NSAIDs in 9 patients, antiulcer drugs in 8 patients, purgatives in 6 patients, antiemetics in 3 patients, antianxiety drugs in 2 patients, and hypnotics in 2 patients. Stages of cancer were stage III in 2 patients, stage IV in 7 patients. Primary cancer locations were esophagus in 3 patients, stomach in 2 patients, biliary tract in 1 patient, colon in 1 patient, ovary in 1 patient, and pharynx in 1 patient (Table 3). The release rates of FP dose immediately before switching FP to morphine injection were 12.5 μg/h in 1 patient, 25 μg/h in 1 patient, 37.5 μg/h in 1 patient, 50 μg/h in 2 patients, 75 μg/h in 1 patient, 100 μg/h in 1 patient, and 150 μg/h in 2 patients (data not shown).

The laboratory test values of ALT, AST, γ-GTP, Scr, and

Table 1. Comparison of Patient Characteristics in Cancer Cachexia and Non-cancer-cachexia Groups at the Start of FP Treatment

	Non-cancer-cachexia ($n = 47$)	Cancer cachexia ($n = 30$)	p-Value
Gender (male/female)	25/22	21/9	0.142[a]
Age (years)	65.8 ± 1.71	61.0 ± 1.88	0.072[b]
FP dose (μg/h)	14.6 ± 0.69	15.7 ± 0.99	0.498[c]
Type of FP			
24 h-acting (Fentos® tape)	19	11	0.742[a]
72 h-acting (Durotep® MT patch)	28	19	
ALT (IU/L)	37.3 ± 5.78	28.3 ± 3.58	0.189[b]
AST (IU/L)	39.9 ± 5.75	37.4 ± 7.55	0.792[b]
γ-GTP (IU/L)	108.0 ± 13.5	100.9 ± 18.8	0.618[b]
Scr (mg/dL)	0.97 ± 0.13	0.71 ± 0.06	0.064[b]
Ccr (mL/min)	79.3 ± 7.09	81.9 ± 5.97	0.795[b]
Concomitant drugs			
NSAIDs	47	30	
Antiulcer drugs	42	28	
Antianxiety drugs	8	6	0.987[a]
Hypnotics	14	9	
Antiemetics	13	6	
Purgatives	42	25	
Cancer stage			
III	6	8	0.295[a]
IV	31	22	
Primary cancer location			
Lung	7	2	
Breast	6	2	
Biliary tract	5	2	
Esophagus	4	6	
Liver	4	2	
Bladder	3	2	0.919[a]
Colon	3	2	
Stomach	3	4	
Ovary	2	1	
Pancreas	2	2	
Uterine cervix	2	1	
Other	6	4	
Opioids prior to FP treatment			
Oral morphine	12	12	0.181[a]
Oral oxycodone	35	18	
MED prior to FP treatment	30.5 ± 2.25	34.7 ± 3.43	0.371[c]

FP: transdermal fentanyl patch; ALT: aspartate transferase; ALT: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; Scr: serum creatinine; NSAIDs: non-steroidal anti-inflammatory drugs; MED: morphine equivalent dose. Ccr was estimated using Cockcraft–Gault equation. Laboratory data are presented as mean ± standard error. *a*) Chi-squared test, *b*) Student's *t*-test, *c*) Mann–Whitney *U* test.

Table 2. Comparison of Patient Characteristics in Cancer Cachexia and Non-cancer-cachexia Groups on Day 7 after FP Treatment

	Non-cancer-cachexia ($n=47$)	Cancer cachexia ($n=30$)	p-Value
ALT (IU/L)	35.6 ± 5.05	29.4 ± 3.82	0.331[a]
AST (IU/L)	39.1 ± 5.43	35.7 ± 6.83	0.694[a]
γ-GTP (IU/L)	106.2 ± 12.7	104.1 ± 18.5	0.707[a]
Scr (mg/dL)	0.89 ± 0.11	0.70 ± 0.06	0.218[a]
Ccr (mL/min)	78.4 ± 6.40	82.4 ± 6.01	0.675[a]
FP dose (μg/h)	16.8 ± 0.95	25.6 ± 1.81	< 0.01[b]
Pain intensity	2.72 ± 0.16	3.17 ± 0.22	0.082[b]
MED	43.3 ± 2.76	75.3 ± 6.30	< 0.01[b]

FP: transdermal fentanyl patch; ALT: aspartate transferase; ALT: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; Scr: serum creatinine; MED: morphine equivalent dose. Ccr was estimated using Cockcraft–Gault equation. Laboratory data are presented as mean ± standard error. *a*) Student's *t*-test, *b*) Mann–Whitney *U* test.

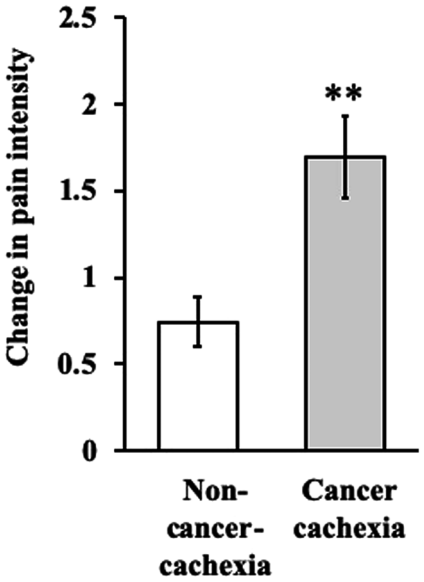

Fig. 1. Comparison of Change in Pain Intensity for 7 d Following FP Treatment in Cancer Cachexia and Non-cancer-cachexia Groups

All measurements of pain intensity for 7 d after commencing FP treatment were considered, and the amount of the change in pain intensity for each patient was calculated by subtracting the minimum measurement from the maximum measurement of pain intensity. Values are presented as mean ± standard error. $^{**}p<0.01$, Mann–Whitney *U* test.

Ccr immediately before the administration of morphine injection were not significantly different from those on day 3 after morphine injection. However, the mean pain intensity and MED on day 3 after morphine injection were significantly lower than those immediately before morphine injection (Table 3).

TEWL by Group Of the 15 patients who provided informed consent, 7 were assigned to the cancer cachexia group, and the remaining 8 patients constituted the non-cancer-cachexia group (Table 4). There were no significant differences in gender, age, type of FP, FP initial dose, ALT, AST, γ-GTP, Scr, Ccr, use of concomitant drugs, stage of cancer, or primary cancer location between the two groups. However, the mean TEWL in the cancer cachexia group was significantly lower than that in the non-cancer-cachexia group (Table 4).

Table 3. Comparison of Patient Characteristics before and after Switching from FP to Morphine Injection

	Before	After	p-Value
Gender (male/female)	6/3		–
Age (years)	56.8 ± 7.6		–
ALT (IU/L)	36.2 ± 10.3	41.1 ± 10.9	0.118[a]
AST (IU/L)	43.1 ± 11.5	41.3 ± 9.13	0.543[a]
γ-GTP (IU/L)	111.2 ± 17.4	115.9 ± 13.3	0.313[a]
Scr (mg/dL)	0.64 ± 0.12	0.65 ± 0.11	0.488[a]
Ccr (mL/min)	100.7 ± 13.3	96.7 ± 12.1	0.169[a]
Concomitant drugs			
NSAIDs	9		
Antiulcer drugs	8		
Purgatives	6		–
Antiemetics	3		
Antianxiety drugs	2		
Hypnotics	2		
Cancer stage			
III	2		–
IV	7		
Primary cancer location			
Esophagus	3		
Stomach	2		
Biliary tract	1		–
Colon	1		
Ovary	1		
Pharynx	1		
Pain intensity	5.78 ± 0.40	4.56 ± 0.44	0.031[b]
MED	338.7 ± 78.1	184.8 ± 35.5	0.021[b]

FP: transdermal fentanyl patch; ALT: aspartate transferase; ALT: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; Scr: serum creatinine; NSAIDs: non-steroidal anti-inflammatory drugs; MED: morphine equivalent dose. Patient characteristics immediately before and on day 3 after administration of morphine injection were compared. Laboratory data are presented as mean ± standard error. *a*) Paired *t*-test, *b*) Wilcoxon signed-rank test.

DISCUSSION

The objective of this study was to evaluate the influence of cancer cachexia on pain control in cancer patients receiving FP, and to investigate whether dry skin was a factor related to cancer cachexia and uncontrolled pain.

First, we retrospectively investigated pain intensity and MED in cancer cachexia and non-cancer-cachexia groups defined according to EPCRC criteria. The FP dose, MED, and change in pain intensity in the cancer cachexia group were significantly higher than those in the non-cancer-cachexia group, although the mean pain intensity on day 7 after FP administration in the cancer cachexia group was not significantly different from that in the non-cancer-cachexia group (Table 2, Fig. 1). The greater variation in pain intensity in the cancer cachexia group suggests that cancer cachexia might be a factor leading to poor pain control. Additionally, our observations suggest that patients with cancer cachexia may need a higher opioid dose to control pain than patients with no cancer cachexia.

Next, to investigate whether poor pain control in cancer cachexia patients receiving FP treatment was caused by decreased transdermal absorption of fentanyl, the change in pain intensity and MED between before and after switching FP to morphine injection in the cancer cachexia group were investigated. The mean pain intensity and MED on day 3 after

Table 4. Comparison of Transepidermal Water Loss in Cancer Cachexia and Non-cancer-cachexia Groups at the Onset FP Treatment

	Non-cancer-cachexia ($n = 8$)	Cancer cachexia ($n = 7$)	p-Value
Gender (male/female)	5/3	5/2	0.714[a]
Age (years)	62.0 ± 1.84	64.6 ± 1.97	0.358[b]
Type of FP			
24 h-Acting (Fentos® tape)	3	3	0.833[a]
72 h-Acting (Durotep® MT patch)	5	4	
FP initial dose (μg/h)	15.2 ± 1.84	14.9 ± 1.85	0.938[c]
ALT (IU/L)	43.9 ± 8.98	42.4 ± 9.94	0.915[b]
AST (IU/L)	46.4 ± 8.66	32.0 ± 4.69	0.185[b]
γ-GTP (IU/L)	88.1 ± 11.6	82.6 ± 16.0	0.788[b]
Scr (mg/dL)	0.81 ± 0.05	0.85 ± 0.04	0.592[b]
Ccr (mL/min)	77.9 ± 4.45	70.1 ± 5.86	0.302[a]
Concomitant drugs			
NSAIDs	8	7	
Antiulcer drugs	8	7	
Antianxiety drugs	2	2	0.997[a]
Hypnotics	2	2	
Antiemetics	2	3	
Purgatives	6	5	
Cancer stage			
III	2	2	0.876[a]
IV	6	5	
Primary cancer location			
Lung	0	1	
Breast	1	0	
Biliary tract	1	0	0.499[a]
Esophagus	2	3	
Colon	3	2	
Stomach	0	1	
Pancreas	1	0	
Transepidermal water loss (TEWL, g/m^{2}h)	12.27 ± 1.70	7.53 ± 0.85	0.029[c]

FP: transdermal fentanyl patch; ALT: aspartate transferase; ALT: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; Scr: serum creatinine; NSAIDs: non-steroidal anti-inflammatory drugs. Ccr was estimated using Cockcraft–Gault equation. Laboratory data are presented as mean ± standard error. *a*) Chi-squared test, *b*) Student's *t*-test, *c*) Mann–Whitney *U* test.

morphine injection were significantly lower than those immediately before morphine injection (Table 3). This result is due to the change in the route of opioid administration from transdermal to intravenous, suggesting that patients with cancer cachexia may experience decreased transdermal absorption of fentanyl; thus, increased MED and poor pain control in patients receiving FP treatment may be due to cancer cachexia. Additionally, opioid switching may cause an increase in the sensitivity to opioids in the cancer cachexia group, and this may be involved in the decreased MED after switching FP to morphine injection. Further studies using animal models are required to confirm the change in sensitivity to opioids in patients with cancer cachexia.

Subsequently, to investigate whether dry skin was involved in poor pain control in the cancer cachexia group, TEWL was compared between the cancer cachexia and non-cancer-cachexia patients. A previous study reported that the serum fentanyl concentration in rats with dry skin was significantly lower than in rats with normal skin.[10] Dry skin is a common physical sign in advanced cancer patients with cancer cachexia.[5] These studies suggest that dry skin may induce the inhibition of fentanyl transdermal absorption, resulting in poor pain control in patients with cancer cachexia. In this study, we found that the mean TEWL in the cancer cachexia group was significantly lower than that in the non-cancer-cachexia group, implying that dry skin in patients with cancer cachexia was more extensive than in those without cancer cachexia. Additionally, our results suggest that dry skin in the cancer cachexia group may cause poor pain control *via* the inhibition of fentanyl transdermal absorption. Patients with cutaneous diseases such as atopic dermatitis have increased TEWL and dry skin, implying that the patients have decreased skin barrier function and moisture content of the skin.[11] However, Berardesca *et al.* showed that dry skin caused by aging produced decreased TEWL and moisture content of skin in patients without cutaneous disease.[12] Additionally, in a rat dry skin model without cutaneous disease, TEWL in rats with dry skin was decreased by about 50% compared to that in rats without dry skin,[10] this observation is consistent with the result of Berardesca *et al.* Since all subjects in this study did not have skin disease, this suggests that cancer cachexia may cause decreased TEWL.

Patients with cancer cachexia have increased inflammatory cytokines, and the cytokines cause lipid degradation and a decrease in lipid synthesis.[13] Additionally, Sawada *et al.* showed that interleukin 4, an inflammatory cytokine, decreased ceramide which is a lipid component in the skin surface.[14] These results show that interleukin-4 induced by cancer cachexia may cause the decrease in ceramide in skin surface. Since ceramide plays a critical role in water holding properties of stratum corneum,[15] the decline of water holding capability

via decreased ceramide in skin may be involved in dry skin in patients with cancer cachexia.

Our study had some limitations. First, since we did not evaluate skin condition and pain control in the same patients, further studies will be required to verify the relationship between both variables in the same sample. Second, we did not evaluate in this study whether differences between stages of cancer cachexia influence pain control in cancer patients receiving FP. EPCRC classifies cancer cachexia into 3 stages (pre-cachexia, cachexia, and refractory cachexia).[8] Particularly, pre-cachexia is at a stage prior to cachexia, and has no characteristic symptoms of cancer cachexia.[8,16] In this study, we classified subjects with cachexia and refractory cachexia into the cachexia group, and classified subjects with non-cachexia and pre-cachexia into the non-cancer cachexia group. Additional studies will be required to evaluate the influence of cachexia stage on pain control in patients receiving FP. Third, this study was a small retrospective study in a single center. Therefore, our findings require validation in a prospective multi-center study with a larger sample.

In conclusion, our data suggest that cancer cachexia may be a risk factor for poor pain control in patients receiving FP treatment, and that uncontrolled pain in FP treatment may be caused by the inhibition of fentanyl transdermal absorption due to dry skin; therefore, pain intensity in patients with cancer cachexia receiving FP should be monitored carefully. Our results are useful for healthcare professionals involved in palliative care.

Conflict of Interest The authors declare no conflict of interest.

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