Cancer Cachexia May Hinder Pain Control When Using Fentanyl Patch

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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 Durrotep® 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 (Durrotep® 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/m²) were significantly lower than in patients with no cachexia (mean BMI, 23 kg/m²).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,3 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.

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
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 (≥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 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 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 Morphine Equivalent Dose (MED)
To compare patients’ opioid daily dose between the cancer cachexia and non-cancer-cachexia groups, transdermal 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   |
| Age (years)              | 65.8 ± 1.71                  | 61.0 ± 1.88              | 0.07²   |
| FP dose (µg/h)           | 14.6 ± 0.69                  | 15.7 ± 0.99              | 0.49²   |
| Type of FP               |                              |                          |         |
| 24 h-acting (Fentos® tape)| 19                          | 11                       | 0.74²   |
| 72 h-acting (Durotep® MT patch)| 28                  | 19                       |         |
| ALT (IU/L)               | 37.3 ± 5.78                  | 28.3 ± 3.58              | 0.18³   |
| AST (IU/L)               | 39.9 ± 5.75                  | 37.4 ± 7.55              | 0.79³   |
| γ-GTP (IU/L)             | 108.0 ± 13.5                 | 100.9 ± 18.8             | 0.61³   |
| Scr (mg/dL)              | 0.97 ± 0.13                  | 0.71 ± 0.06              | 0.06³   |
| Ccr (mL/min)             | 79.3 ± 7.09                  | 81.9 ± 5.97              | 0.79³   |
| Concomitant drugs        |                              |                          |         |
| NSAIDs                   | 47                           | 30                       |         |
| Antiulcer drugs          | 42                           | 28                       |         |
| Antianxiety drugs        | 8                            | 6                        | 0.98³   |
| Hypnotics                | 14                           | 9                        |         |
| Antiemetics              | 13                           | 6                        |         |
| Purgatives               | 42                           | 25                       |         |
| Cancer stage             |                              |                          |         |
| III                      | 6                            | 8                        | 0.29³   |
| 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                        | 0.91³   |
| 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                       | 0.18³   |
| Oral oxycodone           | 25                           | 18                       |         |
| MED prior to FP treatment| 30.5 ± 2.25                  | 34.7 ± 3.43              | 0.37³   |

FP: transdermal fentanyl patch; ALT: aspartate transferase; AST: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; Scr: serum creatinine; NSAIDs: non-steroidal anti-inflammatory drugs; MED: morphine equivalent dose. Ccr was estimated using Cockcroft–Gault equation. Laboratory data are presented as mean ± standard error. a) Chi-squared test, b) Student’s t-test, c) Mann–Whitney U 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 switching from FP to morphine injection were not significantly different from those on day 7 after FP administration in the cancer cachexia group.

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

| Characteristic | Non-cancer-cachexia | Cancer cachexia | p-Value |
|----------------|---------------------|----------------|---------|
| Gender (male/female) | 6/3 | – | – |
| Age (years) | 56.8 ± 7.6 | 56.8 ± 7.6 | 0.01 |
| ALT (IU/L) | 36.2 ± 10.3 | 41.1 ± 10.9 | 0.118 |
| AST (IU/L) | 43.1 ± 11.5 | 41.3 ± 9.13 | 0.543 |
| γ-GTP (IU/L) | 111.2 ± 17.4 | 115.9 ± 13.3 | 0.313 |
| Scr (mg/dL) | 0.64 ± 0.12 | 0.65 ± 0.11 | 0.488 |
| Ccr (mL/min) | 100.7 ± 13.3 | 96.7 ± 12.1 | 0.169 |

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

| Characteristic | Before | After | p-Value |
|----------------|--------|--------|---------|
| Gender (male/female) | 6/3 | 5/4 | 0.125 |
| Age (years) | 56.8 ± 7.6 | 56.8 ± 7.6 | 0.985 |
| ALT (IU/L) | 36.2 ± 10.3 | 41.1 ± 10.9 | 0.118 |
| AST (IU/L) | 43.1 ± 11.5 | 41.3 ± 9.13 | 0.543 |
| γ-GTP (IU/L) | 111.2 ± 17.4 | 115.9 ± 13.3 | 0.313 |
| Scr (mg/dL) | 0.64 ± 0.12 | 0.65 ± 0.11 | 0.488 |
| Ccr (mL/min) | 100.7 ± 13.3 | 96.7 ± 12.1 | 0.169 |

FP: transdermal fentanyl patch; ALT: aspartate transaminase; ALAT: alanine transaminase; γ-GTP: γ-glutamyl transpeptidase; Scr: serum creatinine; 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. **p < 0.01, Mann–Whitney U test. 

**Table 1. Comparison of Laboratory Data**

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

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).
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. However, Berardesca et al. showed that dry skin caused by aging produced decreased TEWL and moisture content of skin in patients without cutaneous disease, TEWL in rats with dry skin was decreased by about 50% compared to that in rats without dry skin, 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. Additionally, Sawada et al. showed that interleukin 4, an inflammatory cytokine, decreased ceramide which is a lipid component in the skin surface. 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, the decline of water holding capability

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<sup>a</sup> |
| Age (years)              | 62.0 ± 1.84                 | 64.6 ± 1.97            | 0.358<sup>b</sup> |
| Type of FP               |                             |                        |         |
| 24h-Acting (Fentos<sup>®</sup> tape) | 3                           | 3                      | 0.833<sup>c</sup> |
| 72h-Acting (Durostep<sup>®</sup> MT patch) | 5                           | 4                      |         |
| FP initial dose (µg/h)   | 15.2 ± 1.84                 | 14.9 ± 1.85            | 0.938<sup>a</sup> |
| ALT (IU/L)               | 43.9 ± 8.98                 | 42.4 ± 9.94            | 0.915<sup>b</sup> |
| AST (IU/L)               | 46.4 ± 8.66                 | 32.0 ± 4.69            | 0.185<sup>b</sup> |
| γ-GTP (IU/L)             | 88.1 ± 11.6                 | 82.6 ± 16.0            | 0.788<sup>b</sup> |
| Scr (mg/dL)              | 0.81 ± 0.05                 | 0.85 ± 0.04            | 0.592<sup>b</sup> |
| Ccr (mL/min)             | 77.9 ± 4.45                 | 70.1 ± 5.86            | 0.302<sup>b</sup> |

Concomitant drugs

- NSAIDs
- Antulcer drugs
- Antianxiety drugs
- Hypnotics
- Antiemetics
- Purgatives

Cancer stage

|   | III | IV |
|---|-----|----|
|   | 2   | 2  | 0.876<sup>a</sup> |
|   | 6   | 5  |         |

Primary cancer location

|   | Lung | Breast | Biliary tract | Esophagus | Colon | Stomach | Pancreas |
|---|------|--------|---------------|-----------|-------|---------|----------|
|   | 0    | 1      | 0             | 0         | 3     | 2       | 0        |

Transepidermal water loss (TEWL, g/m²/h)

|   | Non-cancer-cachexia | Cancer cachexia | p-Value |
|---|---------------------|----------------|---------|
|   | 12.27 ± 1.70        | 7.53 ± 0.85    | 0.029<sup>c</sup> |

<sup>a</sup> Chi-squared test, <sup>b</sup> Student’s t-test, <sup>c</sup> Mann–Whitney U test.

FP: transdermal fentanyl patch; ALT: aspartate transferase; AST: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; Scr: serum creatinine; NSAIDs: non-steroidal anti-inflammatory drugs. Ccr was estimated using Cockcroft–Gault equation. Laboratory data are presented as mean ± standard error.
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). 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 multicenter 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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