Cancer pain is one of the most frequent and distressing symptoms associated with cancer and has a serious impact on the QOL of patients. However, inadequate pain treatment has also been reported in outpatients with cancer pain. The aims of this study were (1) to evaluate the relationship between pain intensity using the Numerical Rating Scale (NRS) and QOL scores using the Japanese version of the European Organization for Research and Treatment of Cancer (QOL Questionnaire Core 15 for Palliative Care (QLQ-C15-PAL)), and (2) to investigate their association with various pain patterns, especially with baseline and breakthrough pain. Forty outpatients who were receiving opioid therapy and obtained informed consent participated. We collected a total of 222 pharmacist consultations during the study period. Global QOL scores and pain scores (PA) in the QLQ-C15-PAL (PA score, 0–100) at the first visit were significantly correlated with worst pain intensity. In addition, the scores for the worst pain were significantly correlated with not only physical functioning scores but also with emotional functioning scores. The correlations between the worst pain NRS and PA scores were positive. Specifically, patients tended to report large variability of NRS scores when the PA score was less than 40 and also when they exhibited pain patterns with “baseline and breakthrough cancer pain in the same day” or “baseline pain throughout the day.” Reducing the worst pain NRS and relieving breakthrough pain appear to be important measures to improve the QOL of outpatients receiving opioid therapy for cancer pain.

Key words QOL; outpatient; numerical rating scale; pain intensity; Questionnaire Core 15 for Palliative Care

INTRODUCTION

Patients with cancer regularly experience various physical and psychological symptoms, and pain is one of the most frequent and distressing symptom. Cancer pain can seriously impact the QOL of patients. Clinical settings for cancer chemotherapy and pharmaceutical care are shifting from in-hospital to outpatient settings, and the number of outpatients with cancer receiving chemotherapy and/or opioid therapy has been increasing. Several studies have observed pain symptoms in 27% or 60% of outpatients with cancer; however, inadequate pain treatment has also been reported in 65% of outpatients. Therefore, appropriate evaluation of pain is essential for both pain management and QOL improvement.

Clinicians often find it difficult to quantify patients’ pain symptoms, and a variety of rating scales have developed to facilitate clinical inquiries into pain intensity. These scales are especially necessary for patients with cancer who are treated with opioid analgesics. Patient-reported outcomes (PROs), which are measurements reported directly by patients, have been considered a good tool to describe subjective symptoms among patients, such as pain severity. The numerical rating scale (NRS), one of the PRO scales, requires patients to verbally assign scores ranging from 0 to 10, which correspond to their current experience of pain. While NRS is helpful for assessing current pain intensity, it is reported that multiple measures evaluating the complex causes and consequences of pain are needed.

We previously reported that pain evaluation using the NRS during opioid treatment in combination with repeated pharmacist interviews and telephone counseling improved pain relief among outpatients with cancer. However, our previous study did not focus on the relationship between pain and QOL.

Regardless of how pain was self-reported by patients, several studies have been reported to provide unique and valuable information on patients’ pain. However, little is known about the relationships among the different types of measurements for self-reported outcomes by patients. Examining such relationship between NRS and QOL questionnaires would provide new information on the utility of using these methods to ensure appropriate pain control, as well as how this association varies with the patterns of pain, especially baseline and breakthrough pain.

The aims of this study were (1) to evaluate the relationship between pain intensity and QOL scores for an appropriate combination of these scores for pain evaluation, and (2) to investigate their association with various pain patterns, especially with baseline and breakthrough pain.

PATIENTS AND METHODS

Patients This was a prospective observational study conducted to use data during routine consultations between pharmacists and outpatients (i.e., pharmacist interventions). To clearly confirm the agreements of the patients, written informed consents were obtained from each patient after the ob-
jectives of this study were explained to them by pharmacists. The pharmacist interventions were performed as part of routine pharmaceutical care before patients received consultations with physicians. The interventions were continued each time a patient visited the hospital, as well as through telephone counseling, as reported in our previous study. All the study participants were outpatients receiving opioid therapy for management of cancer pain at Osaka-fu Saiseikai Noe Hospital from October 2014 to March 2017. The inclusion criteria were as follows: 1) received opioid therapy for cancer pain, 2) had the ability to answer the questionnaires, and 3) consented to participate in this study. The exclusion criterion was that patients were unable to answer the questionnaires due to loss of consciousness or cognitive impairment. This study was approved by the Ethics Committees of Noe Hospital (approved on September 30, 2014) and Kyoto Pharmaceutical University (No. 2017-06). The study period was appropriately extended by the Ethics Committees.

**Measurements** All measurements were obtained from eligible patients during routine pharmacist consultations prior to their physician consultation on the same day. Before each consultation, patients were asked to complete the Japanese version of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C15-PAL), a self-report tool consisting of 10 domains with 15 items, that was developed to evaluate patients’ QOL regarding physical functioning (PF; 3 items of walking condition, living condition, and independence of activity of daily living), emotional functioning (EF; 2 items of tense and depressed), dyspnea (DY), pain (PA; 2 items of presence of pain and interference with activity by pain), insomnia (SL), appetite loss (AP), constipation (CO), fatigue (FA; 2 items of weak and tired), nausea and vomiting (NV), and overall QOL. Patients were asked to respond to each item with reference to their condition over the previous 7 days using a 4-point scale (1 = not at all, 4 = very much) for the two functional scales and seven symptom scales and a 7-point scale (1 = very poor, 7 = excellent) for overall QOL. All domains were linearly transformed according to a previous publication with transformed scores ranging from 0 to 100.

After patients completed the QLQ-C15-PAL, pharmacists asked them to provide ratings on an NRS ranging from 0 to 10 for three specific pain intensities within a day—worst, average, and least pain—without referring to the QLQ-C15-PAL to ensure independence between the measures. Pharmacists also asked patients to select one of the following pain patterns: (a) no pain; (b) breakthrough cancer pain occurring several times per day; (c) baseline and breakthrough cancer pain on the same day; and (d) baseline pain throughout the day.

Other data, including sex, age, performance status (PS), cancer type, opioid analgesic type(s), daily around-the-clock

| Table 1. Basic Patient Characteristics |
|---------------------------------------|
| Number of patients | 40 (20 male/20 female) |
| Age (years, median), range (minimum–maximum) | 67, 35–87 |
| Performance status, 0/1/2/3 | 29/8/2/1 |
| Cancer types | Number of patients |
| Colorectal | 13 |
| Breast | 8 |
| Lung | 6 |
| Gastric | 5 |
| Pancreas | 3 |
| Others (bile duct, ovarian, prostate, ureteral, thyroid) | 1 each (total = 5) |
| Opioids | Number of patients, and morphine equivalent daily dose (mg) |
| Oxycodone tablet (OxyContin®) | 26* (7.5–300 mg) |
| Fentanyl transdermal (One Duro®) | 9* (60–240 mg) |
| Methadone tablet (Methapain®) | 1 (30 mg as methadone hydrochloride) |
| Not around-the-clock | 5 |
| Rescues | Number of patients, and morphine equivalent daily dose for single use (mg) |
| Oxycodone granules (Oxinorm®) | 29 (3.75–60 mg) |
| Morphine solution (Opso®) | 3 (5 mg) |
| Other analgesics | Number of patients |
| NSAIDs | 20 |
| Acetaminophen | 9 |
| Transformed scores of the QLQ-C15-PAL | Mean ± S.D. |
| Physical Functioning (PF) | 62.9 ± 27.1 |
| Emotional Functioning (EF) | 70.7 ± 27.3 |
| Dyspnea (DY) | 21.1 ± 29.2 |
| Pain (PA) | 43.1 ± 32.8 |
| Insomnia (SL) | 31.6 ± 36.6 |
| Appetite Loss (AP) | 32.5 ± 29.6 |
| Constipation (CO) | 26.1 ± 28.3 |
| Fatigue (FA) | 46.5 ± 28.1 |
| Nausea and Vomiting (NV) | 12.0 ± 24.2 |
| QOL | 50.5 ± 26.0 |

Abbreviations: NSAIDs: nonsteroidal anti-inflammatory drugs, QLQ-C15-PAL: Quality of Life Questionnaire Core 15 for Palliative Care, S.D.: standard deviation. *One patient was taking oxycodone tablets and transdermal fentanyl.
opioid analgesic doses, rescue doses for breakthrough cancer pain, and other analgesics used were also collected from the patient’s electronic medical records.

**Data Analysis**  NRS and QLQ-C15-PAL scores were presented as means and standard deviations (S.D.). Correlations between NRS and QLQ-C15-PAL scores were determined using Spearman’s correlation coefficients (\( \rho \)) using data at the first visit for each patient. The correlation coefficient of <0.30 indicates a weak relationship, 0.30–0.50 a moderate relationship, and >0.50 a strong relationship. The relationship between NRS scores of the three pain intensities, that is, worst, average, and least pain, and PA scores in the QLQ-C15-PAL were plotted with different symbols for the different patterns of pain.

Data were summarized using Microsoft Excel, and all statistical analyses were performed using the Bell Curve for Excel 2.15 (Social Survey Research Information Co., Ltd.). The significance level was set at 0.05 or 0.01 for the analysis.

**RESULTS**

We obtained the eligible data from 40 patients. The basic characteristics of 40 patients with cancer pain receiving opioid therapy are shown in Table 1. As shown in Table 1, 50% of the patients were male, with a median age of 67 years and the following cancer types: colon cancer (32.5%, 13/40), breast cancer (20.0%, 8/40), lung cancer (15.0%, 6/40), and gastric cancer (12.5%, 5/40). Most patients (92.5%, 37/40) had a PS of 0 or 1, which was probably attributable to their outpatient status. The most commonly administered opioid formulation was sustained-release oxycodone tablets (65.0%, 26/40), while five patients required no around-the-clock dosages for the control of cancer pain.

Table 2 shows the Spearman rank correlation between the NRS and QLQ-C15-PAL scores. During the study period, each outpatient underwent between 1 and 20 pharmacist consultations, and we collected a total of 222 pharmacist consultations. To avoid a bias by the different numbers of measurements among patients, we used the data only the first visit for each patient to estimate the correlation coefficients. Global QOL score and PA were significantly correlated with the worst pain scores. Concerning the correlation between the worst pain NRS and other QLQ-C15-PAL scores, there were strong correlation for FA (\( \rho = 0.51 \)), and moderate correlations for EF (\( \rho = -0.46 \)), SL (\( \rho = 0.38 \)), and PF (\( \rho = -0.33 \)). No other significant correlations were found for the average and least pain scores.

Table 3 summarizes the pain scores (both NRS and QLQ-C15-PAL) during all pharmacist consultations. Only data of the first visit for each patient were used. \( \rho \): Spearman’s correlation coefficient. Abbreviations: PF: physical functioning, EF: emotional functioning, DY: dyspnea; PA: pain; SL: insomnia; AP: appetite loss; CO: constipation; FA: fatigue; NV: nausea and vomiting. PA: pain score based on two items of presence of pain and interference with activity by pain. Statistically significant *: \( p < 0.05 \), **: \( p < 0.01 \).

Table 2. Correlation between NRS and QLQ-C15-PAL (n = 40)

| Items  | Least pain | | Average pain | | Worst pain | |
|--------|------------|---|--------------|---|-------------|---|
|       | \( \rho \) | \( p \)-Value | \( \rho \) | \( p \)-Value | \( \rho \) | \( p \)-Value |
| PF    | -0.06      | 0.746 | -0.24        | 0.252 | -0.33       | 0.043* |
| EF    | -0.26      | 0.132 | -0.32        | 0.119 | -0.46       | 0.006** |
| DY    | 0.17       | 0.311 | 0.15         | 0.490 | 0.14        | 0.424 |
| PA    | 0.20       | 0.259 | 0.47         | 0.020* | 0.71        | <0.001** |
| SL    | -0.01      | 0.941 | 0.08         | 0.708 | 0.38        | 0.020* |
| AP    | 0.11       | 0.537 | -0.09        | 0.681 | 0.02        | 0.894 |
| CO    | -0.05      | 0.756 | 0.10         | 0.633 | 0.21        | 0.216 |
| FA    | 0.24       | 0.176 | 0.35         | 0.092 | 0.51        | 0.002** |
| NV    | -0.04      | 0.794 | 0.05         | 0.799 | 0.26        | 0.117 |
| QOL   | -0.27      | 0.120 | -0.36        | 0.078 | -0.36       | 0.031* |

Table 3. Summary of the Pain Scores during All Pharmacist Consultations

| Items  | First visits' data | | All data | |
|--------|-------------------|---|-----------|---|
|        | Range | Mean ± S.D. | Range | Mean ± S.D. |
| NRS (range: 0–10) | | | | |
| Worst pain | 0–10 | 4.9 ± 3.0 | 0–10 | 4.2 ± 2.9 |
| Average pain | 0–8 | 3.5 ± 2.4 | 0–8 | 2.7 ± 2.1 |
| Least pain | 0–8 | 1.8 ± 2.1 | 0–8 | 1.2 ± 1.8 |
| QLQ-C15-PAL | | | | |
| PA | 0–100 | 42.8 ± 32.2 | 0–100 | 30.6 ± 23.3 |
| Pattern of pain (n = 38)* | | | | |
| (a) No pain | 6 | 66 | |
| (b) Breakthrough pain several times in a day | 20 | 116 | |
| (c) Baseline pain and breakthrough pain in a day | 9 | 23 | |
| (d) Baseline pain all day | 3 | 15 | |

* Pain pattern data were missing for two patients. Abbreviations: NRS: Numerical Rating Scale, QLQ-C15-PAL: Quality of Life Questionnaire Core 15 for Palliative Care, PA: pain score based on two items of presence of pain and interference with activity by pain, S.D.: standard deviation.
QLQ-C15-PAL) and pain patterns determined during the 222 pharmacist consultations. Both the summaries for the first visits \( (n = 40) \) and all data \( (n = 222) \) were shown. The mean of the worst pain NRS was 4.2 (S.D.: 2.9), while the worst pain NRS score >4 \( (i.e., \text{moderate pain}^{19}) \) was reported in approximately 50% \( (106/222) \) of the consultations. The mean PA on the QLQ-C15-PAL was 30.6 (S.D.: 23.3). Among the 220 pain pattern measurements (two were missing), the pattern reported most frequently was pattern b (breakthrough cancer pain occurring several times per day; 52.7%, 116/220), followed by pattern c (baseline pain and breakthrough pain in the same day; 10.5%, 23/220) and pattern d (baseline pain all day; 6.8%, 15/220). Given that patterns a or b had been reported in 82.7% \( (182/220) \) of the consultations, baseline pain appeared to be generally controlled.

Figure 1 shows the individual plots for the scores between NRS scores of the worst, average and least pain and PA on the QLQ-C15-PAL scores for data of the first visit (Figs. 1. Individual Plots of the Scores for Data of the First Visit ((A)-(C)) and All Data ((D)-(F)) of the Worst, Average and Least Pain Scores of the NRS Relative to Pain Scores (PA) in QLQ-C15-PAL

The plots were randomly jittered to avoid superimposition. Different colors were used to indicate each type of pain: white (a) no pain; light gray (b) breakthrough cancer pain occurring several times per day; gray (c) baseline and breakthrough cancer pain in the same day; and black (d) baseline pain throughout the day. NRS: Numerical Rating Scale; QLQ-C15-PAL, Quality of Life Questionnaire Core 15 for Palliative Care. PA: pain score based on the items of presence of pain and interference with activity by pain.
I(A)–(C)) and for all data (Figs. I(D)–(F)). Both data showed similar patterns. As for the relationship between worst pain NRS and PA, the plots showed a large variability in the NRS scores (ranging from 0 to 10) when PA was <40, especially for pain patterns b or c. In contrast, patients tended to report worst pain NRS scores >5 (moderate pain) when their PA scores were >60, for pain patterns b, c, or d. In the relationship between the least pain NRS score and PA, most of the plots showed 0 or 1 for the least pain when the pain pattern was b, regardless of the PA score. On the other hand, the plots showed at least 4 for least pain when the pain pattern was d.

DISCUSSION

We examined the relationship between pain and QOL of outpatients with cancer pain receiving opioid therapy. Patients completed the QLQ-C15-PAL and indicated their pain based on three pain intensities (worst, average, and least pain) using NRS and pain patterns. Our results indicated that especially worst pain intensity was associated with global QOL. There was a moderate correlation for worst pain, not only PF ($\rho = -0.33$), but also EF ($\rho = -0.46$). In addition, worst pain showed correlations with distress symptoms such as fatigue and insomnia. These results suggest that reducing the level of worst pain would improve not only physical function but also emotional function. Although NRS is often used when evaluating a patient’s response to an increased dose of analgesic, our result showed new information for pain management by combination of NRS, pattern of pain and QLQ-C15-PAL scores. It has been reported that pain, fatigue and appetite loss, which are the three most common symptoms of patients with advanced cancer, were significantly related to patients’ QOL scores. Another study showed that fatigue strongly influenced QOL in patients with advanced cancer. These results coincided with our results and relieving pain and fatigue is important for improving the QOL of outpatients with cancer pain who are receiving opioid therapy.

Moreover, we investigated the association between pain intensity, including pain patterns, that is, presence and absence of baseline and breakthrough pain, and PA. At first, pain intensity and PA showed a high correlation ($\rho = 0.71$) with worst pain, and a moderate correlation ($\rho = 0.47$) with average pain (Table 2). Although patients generally showed good control of baseline pain (a) + (b), 26/38 sessions; 68.4% at the first visit, and 182/220 sessions; 82.7% for all data), their breakthrough pain was poorly controlled (Table 3). Outpatients tended to report higher NRS scores when PA was high and when they exhibited pain patterns with breakthrough pain (b) and/or baseline pain (c) not only at the first visit but at the continuous consultation.

For pain pattern b or c (Fig. 1), the plots indicated that worst pain NRS scores >4 corresponded to PA scores >60. Lower pain symptom scores (PA <40) have been reported to indicate better physical condition. However, when the PA scores were <40, participants’ NRS scores ranged from 2 to 10, particularly among those with pain patterns b and c. Davies et al. reported that breakthrough cancer pain had a significant negative effect on QOL. These results suggest that the frequency and/or type of breakthrough pain associated with PA. In our study, the pain patterns of outpatients with cancer pain were more likely to experience breakthrough pain. Therefore, the management of breakthrough cancer pain appears to be particularly important for outpatients experiencing cancer pain. Our result revealed the new information for pain management by combination of NRS, pattern of pain and QLQ-C15-PAL scores.

There are some limitations to the present study. The data were limited to those produced by a single hospital and of a small size. Therefore, the present study included subjects with a limited range of cancer types (Table 1) who were taken from the surgery, breast surgery, and respiratory departments of the hospital. Another limitation is that the pain pattern in our study is not necessarily the best method, and the optimal pain assessment should be considered continuously and from a variety of perspectives with appropriate assessment for individual patients with medical team staffs.

CONCLUSION

In this study, we demonstrated that worst pain intensity was associated with global QOL, physical and emotional functions. In addition, the pain patterns of outpatients with cancer pain were more likely to have breakthrough pain. Reducing worst pain and relieving breakthrough pain appear to be important measures to improve the QOL of outpatients receiving opioid therapy for cancer pain.

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Conflict of Interest The authors declare no conflict of interest.

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