**Effect of Continuous Pharmacist Interventions on Pain Control and Side Effect Management in Outpatients with Cancer Receiving Opioid Treatments**

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Received September 19, 2017; accepted March 18, 2018

For improving the QOL of patients diagnosed with cancer, early palliative care is recommended, aiming to minimize pain and opioid-induced side effects. Herein, we evaluated the effect of continuous interventions for pain management and opioid-induced side effects in outpatients with cancer. Pharmacists continuously performed interventions on patients on their hospital visits, starting from the first visit for opioid introduction to intervention via telephone. We recorded their pain patterns and intensities, use of rescue doses, and types and degrees of side effects during these interventions. The physicians were suggested appropriate recommendations for increased doses or alternative opioids when the pharmacists considered the analgesic dose should be titrated. During the study period, palliative care pharmacists conducted 105 interviews for 27 patients (male: 19 and female: 8) with cancer pain. Pain intensities significantly decreased after the pharmacists’ continuous intervention, including those from telephone interviews, with their appropriate recommendations and increased opioid doses. Side effects such as nausea and constipation increased or remained unaffected even after the intervention, likely due to the increased opioid doses. Approximately 90% of recommendations for pain control were accepted by the physicians and helped to control the pain intensities. Before starting physician consultations, pharmacists informed the patients that adequate pain control and side effect management were achievable through regular interviews, wherein patient symptoms were monitored and patients received detailed explanations of pharmaceutical care and courteous and continuous counseling.

**Key words** Pharmacist intervention; palliative care; pain control; opioid; cancer patient

For improving the QOL of patients diagnosed with cancer, early palliative care is recommended to them as well as their caregivers. For patients with advanced lung cancer, early specialized palliative care reportedly produces positive outcomes, such as better QOL and prolonged life. Despite the importance of early palliative care interventions for patients with cancer, they are partially unclear because of the difficulties in integrating palliative care into oncology.

Tumor causes chronic cancer-related pain in many patients with cancer. Accordingly, data from a large-scale prospective survey of cancer pain syndromes suggested that approximately 25% of the patients experienced ≥2 kinds of pain, >90% had ≥1 tumor-related pains, and 20% had ≥1 pain caused by cancer therapies.

For moderate-to-severe pain relief, opioid medications are the main approach. The pain intensities are not adequately evaluated in approximately 50% of patients with cancer. Moreover, opioid side effects, such as nausea, vomiting, and constipation, may be the limiting factors of opioid use and lead to early discontinuation and inadequate analgesic efficacy. Therefore, to achieve good pain management in patients with cancer, it is necessary to minimize pain and opioid side effects.

Several studies have reported educational interventions for improving cancer pain control and multidisciplinary efforts, involving physicians, nurses, and pharmacists, are required for satisfactory cancer pain management. Pharmacist interventions improve the efficacy of cancer chemotherapy, medication adherence, and patient satisfaction.

Despite the demonstrated effects of pharmacist interventions for outpatients with cancer undergoing cancer chemotherapy, their effects on cancer pain control are poorly understood. We have demonstrated that pharmacist interventions improve pain intensity scores and reduce opioid-related side effects in outpatients with cancer by examining the effect of pharmacist interventions at the following instances: (1) the first visit for opioid introduction, (2) telephone interviews and counseling on non-visiting days, and (3) at the second hospital visit. These evaluations revealed decreased pain intensity after the interventions; however, continuous pharmacist interviews for >3 occasions will likely provide better control of pain and side effects. Therefore, we suggest that including continuous pharmacist interventions, comprising continuing interviews, telephone counseling, and direct contact at the hospital before physician consultations, will improve the quality of pharmacist interventions.

Herein, we determined whether continuous pharmacist consultations adequately improved pain management and opioid-induced side effects in outpatients with cancer. Therefore, we performed a prospective observational study to assess the changes of pain intensity scores, degrees of side effects, and changes in total daily doses of opioid analgesics, as well as the types of pharmacist recommendations and physician acceptance rates.
METHODS

Patients We evaluated the effect of pharmacist interventions in outpatients administered with opioid treatments for cancer pain relief at Osaka-fu Saiseikai Noe Hospital (Osaka, Japan). Data from all patients with cancer pain who received pharmacist interventions from October 2014 to March 2016 were included. Patients who did not provide informed consent were excluded. The study protocol was approved by the Ethics Committees of the hospital on September 30, 2014, and the Kyoto Pharmaceutical University (No. 17-06).

Intervention Four pharmacists of the Pharmacy Unit of the hospital performed the interventions. These pharmacists were familiar with palliative care through their routine activities for >5 years; the interventions were started at the first visit of a patient for opioid introduction. After the introduction of opioid analgesics, telephone interviews and counseling were provided to patients at home between 3 and 7 d after the first visit. As the adequate analgesic effect of opioids is usually observed after 48 h of administration and the patients’ next visit was 7 d later, we interviewed the patients between 3 and 7 d for our daily counseling. Pharmacists taught the following items to the patients: how to assess pain intensity and pain response to analgesics, how to treat breakthrough pain using rescue doses, and how to prevent or treat side effects caused by analgesics.

The interventions were performed before physician consultations on visiting days and were repeated on every visit until the patients were hospitalized or no longer visited the hospital. Pharmacists’ interviews comprised questions relating to pain patterns and intensities, use and efficacy of rescue doses, and types and degrees of side effects. The pain intensity was assessed using the numerical rating scale (NRS), and side effects, such as nausea, constipation, drowsiness, and delirium, were evaluated using the Support Team Assessment Schedule Japanese edition (STAS-J). The pain intensity was reported by patients with scores from 0 (no pain) to 10 (worst pain) as the worst pain, the average pain, and the least pain on that day to better understand the pain patterns within a day for comprehensive pain evaluation before physician consultations. The pain intensity was classified into three categories: mild pain (NRS, 0–3), moderate pain (4–6), and severe pain (7–10). The side effects were rated using five categories: 0 (none), 1 (sometimes), 2 (moderate), 3 (frequent), and 4 (severe). When the pharmacists recognized the need of titration of analgesic prescriptions for pain control, i.e., frequent use of rescue dose, continuous severe baseline pain all day despite opioid introduction, incorrect selection of analgesic drugs judged by quality of pain, and impossibility of increasing opioid dose due to opioid-induced side effects, increasing opioid doses or administering alternative opioids was recommended to the physicians. Similarly, when side effect management was not satisfied, pharmacists recommended adequate antiemetic or laxative drugs based on the findings of counseling, such as the nature of stool, the onset of nausea or vomiting, the presence or absence of chemotherapy, or the comparison of grade scores of side effects with their previous scores.

Data Collection At the first interview for opioid introduction, we recorded the patient’s sex and age, as well as cancer type, kinds of opioid analgesics and other analgesics, pain patterns, pain intensity scores, daily doses of around-the-clock (ATC) opioid analgesics, rescue doses for breakthrough pain, and degrees of side effects were recorded. Daily doses of opioids were measured as morphine-equivalent daily doses. At subsequent interviews, pain intensities, degrees of side effects, and daily doses of opioid analgesics were assessed and recorded at subsequent interviews. Daily opioid analgesic doses were calculated as corresponding morphine doses using an oxycodone to morphine conversion ratio of 2:3 or a fentanyl to morphine conversion ratio of 1:100.

Types of Pharmacist Recommendations and Physician Acceptance Rates The pharmacists’ recommendations were as follows: (1) change dose, (2) change medication, (3) initiate new medication, (4) stop current medication, and (5) others. The physician acceptance rates of these recommendations were calculated as follows:

Acceptance rate (%) = number of recommendations accepted / total number of recommendations by pharmacists × 100

Statistical Analysis The number of patients with their respective pain severities and pain changes from the first experience (before intervention) were summarized at each occasion based on the method by Ma et al. In this study, we defined the timing of pharmacist interviews using a term “occasion”; occasion 1 (before intervention), 2 (telephone interview), 3 (second visit), 4 (third visit), 5 (fourth visit) and 6 (fifth visit). The pain changes were categorized as follows: better (pain score was reduced by 2 points or 30%), stable (pain score changed from −1 to +1), and worse (pain score increased by 2 points or more). The relationship between the pain score and pain score change (better, stable, or worse) was examined using Fisher’s exact test; p < 0.05 was considered statistically significant. Data were summarized using Microsoft Excel, and Fisher’s test was performed using R statistical software. The grading scores of nausea and constipation, and morphine equivalent daily dose were compared among the occasions by Friedman’s test.

RESULTS

During the study period, palliative care pharmacists conducted 105 interviews for 27 patients (male: 19 and female: 8) with cancer pain. Table 1 summarizes the patient characteristics. The most common cancer types were gastrointestinal, including colorectal (6, 22.2%), gastric (6, 22.2%), and pancreatic cancer (4, 14.8%). Oxycodone, an opioid analgesic, was prescribed to 23 of the 27 patients (85.2%), and nonsteroidal anti-inflammatory drugs were prescribed in 13 of the 27 patients (48.1%) without stopping upon opioid introduction. Table 2 shows the pain scores and degrees of opioid-induced side effects at opioid introduction. Pain patterns predominantly comprised breakthrough and intermittent baseline pain several times in a day. The median (range) NRS scores of the worst pain, average pain, and least pain were 7.0 (5–10), 4.0 (1–9), and 1.0 (0–9), respectively, and varied widely. One patient had severe baseline pain all day on opioid introduction; therefore, the NRS score of both least and average pain was 9.

Changes of Pain Intensity Scores, Degrees of Side Effects, and Total Doses of Opioid Analgesics Table 3 shows the summary of pain severity and pain score change during different occasions. The numbers of assessments from
each interview varied because the NRS data were not always available for all patients. Upon opioid introduction (occasion 1), 42.3% (11 of 26) and 57.7% (15 of 26) of patients reported moderate pain (NRS, 4–6) and severe pain (NRS, 7–10) as the worst pain, respectively, and 74.1% (20 of 27) reported moderate pain as the average pain. After pharmacists’ intervention, the number of patients reporting severe pain as the worst pain on occasions 1–6 were 15 of 26 (51.7%), 10 of 27 (37.0%), 7 of 24 (29.2%), 4 of 14 (28.6%), 1 of 5 (20.0%), and 1 of 5 (20.0%), respectively. The results of Fisher’s exact test showed a significant change in the worst, average, and least pain scores at occasions 2 and 3 compared with those at occasion 1. Table 3 shows the $p$-values for these combinations.

Side effects such as nausea and constipation were compared with data from patients without missing data at occasions 1 to 3. The grading score for nausea was mostly 0 (20 of 24, 83.3%) before intervention, and two patients reported grades 3 and 4 after opioid introduction. Statistical comparison was performed only for data from patients without missing data at occasions 1 to 3 ($n=18$), suggesting significant difference between occasions 1 and 3 ($p=0.010$), and between occasion 2 and 3 ($p=0.002$).

**DISCUSSION**

In the present study, we determined whether continuous pharmacist interventions are adequately based on actual patient assessments of pain control and side effect management. In our outpatients, pain intensities decreased by appropriate increases in opioid doses at occasions 2 and 3 compared with pre-intervention scores (Table 3, Fig. 1). No statistical compar-

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**Table 1. Patient Characteristics**

| Item                  | Value             |
|-----------------------|-------------------|
| Sex (male/female)     | 19/8 (n=27)       |
| Age                   | Median (range) 71 (50–87) |
| Cancer type           | Colorectal 6 (22.2%) |
|                       | Gastric 6 (22.2%)   |
|                       | Lung 5 (18.5%)      |
|                       | Pancreas 4 (14.8%)  |
|                       | Other 6 (22.2%)     |
| Opioid analgesics     | Morphine (oral tablet) 1 (3.7%) |
|                       | Oxycodone (oral capsule) 23 (85.2%) |
|                       | Fentanyl (transdermal patch) 3 (11.1%) |
| Other analgesics      | NSAIDs* 13 (48.1%) |
|                       | Acetaminophen 0 (0.0%) |
|                       | Adjuvant analgesics 2 (7.4%) |
| Antiemetic            | Prochlorperazine maleate 20 (74.0%) |
|                       | Domperidone 2 (7.4%) |
|                       | Itopride hydrochloride 1 (3.7%) |
|                       | No prescription 4 (14.8%) |
| Laxative              | Magnesium oxide 21 (77.8%) |
|                       | Sennoside 3 (11.1%) |
|                       | Daikenchuto 1 (3.7%) |
|                       | Lubiprostone 1 (3.7%) |
|                       | No prescription 1 (3.7%) |

*NSAIDs: nonsteroidal anti-inflammatory drugs.

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**Table 2. Summary of Scores for Pain and Grades of Side Effects at the First Visit for Opioid Introduction**

| Item                  | Median (range)   |
|-----------------------|------------------|
| Pain score$^{a}$      |                  |
| Least pain            | 1.0 (0–9)        |
| Average pain          | 4.0 (1–9)        |
| Worst pain            | 7.0 (5–10)       |
| Pattern of pain       |                  |
| (a) No pain           | 0                |
| (b) Breakthrough pain several times in a day | 12      |
| (c) Baseline pain and breakthrough pain in a day | 13      |
| (d) Baseline pain all day | 2              |
| Dose of opioids       |                  |
| prescribed on the day of the first occasion$^{b}$ |                  |
| ATC$^{c}$ dose        |                  |
| 0mg                   | 4                |
| 15mg                  | 17               |
| 30mg                  | 5                |
| 45mg                  | 0                |
| 60mg                  | 1                |
| PRN$^{d}$ dose        |                  |
| 0mg                   | 3                |
| 5mg                   | 3                |
| 7.5mg                 | 21               |
| Side effects$^{e}$    |                  |
| Nausea                | 0 (0–2)          |
| Constipation          | 0 (0–4)          |
| Drowsiness            | 0 (0–2)          |
| Delirium              | 0 (0)            |

$^{a}$Pain assessment was performed using a numerical rating scale (NRS). $^{b}$Oral morphine daily dose equivalent. $^{c}$ATC, around-the-clock; PRN, pro re nata (as needed). $^{d}$Assessed using the Support Team Assessment Schedule Japanese edition (STAS-J).
ison was adopted at occasion 5 because the number of patients was small (n=5). The grading score of nausea, and constipation increased or remained unchanged, respectively, likely due to the increased opioid doses during the intervention period. When pharmacists assessed poor pain control, they recommended increased opioid doses or alternative opioids, and physicians adopted these recommendations in approximately 90% of the cases. This high acceptance rate may reflect the present evidence from patient pain and side effect scores, which allowed effective communication with physicians.

During interventions, pharmacists carefully monitored the symptoms of any side effects, particularly nausea, respiratory depression, insomnia, and constipation, and instructed patients how to control them using appropriate medications. Consequently, grading scores for constipation did not increase on later occasions, despite increased opioid doses (Fig. 1).

Opioid-induced side effects usually increased during opioid introduction or with increase in the opioid dose. Based on patient complaints during interviews, the pharmacists’ recommended the use of appropriate medications, such as osmotic laxatives for hardness flights and colon-stimulant laxatives for obstructed defecation. Some patients did not complain of constipation until the pharmacists indicated it as a side effect of

### Table 3. Summary of Pain Severity and Pain Score Change during the Occasions

| Pain severity | Pain score at first occasion (Before intervention) | Pain score at second occasion (Telephone interview) | Pain score at third occasion (Second visit) | Pain score at fourth occasion (Third visit) |
|---------------|---------------------------------------------------|--------------------------------------------------|------------------------------------------|------------------------------------------|
|               | Pain score | Better | Stable | Worse | Pain score | Better | Stable | Worse | Pain score | Better | Stable | Worse | Pain score | Better | Stable | Worse |
|               | n (%)      | n (%)   | n (%)   | n (%)   | n (%)      | n (%)   | n (%)   | n (%)   | n (%)      | n (%)   | n (%)   | n (%)   | n (%)      | n (%)   | n (%)   | n (%)   |
| **Worst pain**|           |        |        |        |            |        |        |        |            |        |        |        |            |        |        |        |
| 0 (No pain)  | 0 (0)      | 2 (7.4)| 2 (100)| 0 (0)  | 1 (4.2)    | 1 (100)| 0 (0)  | 0 (0)  | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  |
| 1–3 (Mild)   | 0 (0)      | 2 (7.4)| 2 (100)| 0 (0)  | 6 (25)     | 6 (100)| 0 (0)  | 0 (0)  | 2 (14.3)   | 2 (100)| 0 (0)  | 0 (0)  | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  |
| 4–6 (Moderate)| 11 (42.3)| 13 (48.1)| 5 (41.7)| 7 (58.3)| 10 (41.7) | 5 (55.6)| 4 (44.4)| 0 (0)  | 8 (57.1)   | 4 (57.1)| 3 (42.9)| 0 (0)  | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  |
| 7–10 (Severe)| 15 (57.7)| 10 (37)| 1 (10) | 6 (60) | 3 (30)    | 7 (29.2)| 0 (0)  | 5 (71.4) | 2 (28.6)   | 4 (28.6)| 0 (0)  | 3 (75) | 1 (25)     |        |        |        |
| **Total**    | 10 (38.5)| 13 (50)| 3 (11.5)|        |           |        |        |        |            |        |        |        |            |        |        |        |
| **Average pain** |          |        |        |        |            |        |        |        |            |        |        |        |            |        |        |        |
| 0 (No pain)  | 0 (0)      | 2 (7.4)| 2 (100)| 0 (0)  | 1 (4.3)    | 1 (100)| 0 (0)  | 0 (0)  | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  |
| 1–3 (Mild)   | 6 (22.2)   | 11 (40.7)| 6 (54.5)| 5 (45.5)| 14 (60.9)| 9 (64.3)| 5 (35.7)| 0 (0)  | 9 (64.3)   | 7 (77.8)| 2 (22.2)| 0 (0)  | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  |
| 4–6 (Moderate)| 20 (22.2)| 11 (40.7)| 1 (9.1) | 10 (90.9)| 0 (0)    | 7 (30.4)| 0 (0)  | 7 (100) | 0 (0)      | 3 (21.4)| 0 (0)  | 3 (100)| 0 (0)     |        |        |        |
| 7–10 (Severe)| 1 (3.7)    | 3 (11.1)| 0 (0)  | 1 (33.3)| 2 (66.7)| 1 (4.3) | 0 (0)  | 0 (0)  | 1 (100)    | 2 (14.3)| 0 (0)  | 0 (0)  | 2 (100)    |        |        |        |
| **Total**    | 9 (33.3)   | 16 (59.3)| 2 (7.4)|        |           |        |        |        |            |        |        |        |            |        |        |        |
| **Least pain** |           |        |        |        |            |        |        |        |            |        |        |        |            |        |        |        |
| 0 (No pain)  | 11 (42.3)  | 11 (40.7)| 4 (36.4)| 7 (63.6)| 0 (0)    | 10 (41.7)| 3 (30.0)| 7 (70)| 0 (0)      | 6 (42.9)| 2 (33.3)| 4 (66.7)| 0 (0)     |        |        |        |
| 1–3 (Mild)   | 12 (46.2)  | 12 (44.4)| 2 (18.2)| 8 (72.7)| 1 (9.1)  | 12 (50) | 2 (18.2)| 9 (81.8)| 0 (0)      | 5 (35.7)| 1 (25) | 3 (75) | 0 (0)     |        |        |        |
| 4–6 (Moderate)| 2 (7.7)   | 3 (11.1)| 1 (33.3)| 0 (0)  | 2 (66.7)| 1 (4.2) | 0 (0)  | 0 (0)  | 1 (100)    | 3 (21.4)| 0 (0)  | 0 (0)  | 3 (100)    |        |        |        |
| 7–10 (Severe)| 1 (3.8)    | 1 (3.7)| 0 (0)  | 1 (100) | 1 (4.2)  | 0 (0)  | 0 (0)  | 1 (100) | 0 (0)      | 0 (0)  | 0 (0)  | 0 (0)  | 0 (0)     |        |        |        |
| **Total**    | 7 (26.9)   | 15 (57.7)| 4 (15.4)|        |           |        |        |        |            |        |        |        |            |        |        |        |

*p = 0.001*  
*p = 0.0001*  
*p = 0.0001*  
*p = 0.015*  

Table 3. Summary of Pain Severity and Pain Score Change during the Occasions

Pain severity on occasion 1 was compared to that on occasion 2–4 in statistical analysis. Data for worst pain and least pain in one patient were missing at the first occasion and were not included for evaluation of pain score change.

![Fig. 1. Plots of Morphine-Equivalent Daily Doses Presented as Mean and Standard Deviations (Black Symbols) and Those in Individual Patients (Gray Symbols) during Pharmacists’ Intervention](image-url)
opioids, suggesting that courteous and continuous interviews and counseling are effective management tools for assessing the side effects. To evaluate constipation, it would have been important to interview about their dietary intake, although we did not include this in the interview in this study.

In the study by Ma et al., opioids, which constituted 80% of the patients had previously used long-acting opioids. In contrast, we investigated the effect of intervention at opioid introduction; therefore, the significant effect of the intervention was observed in our study. Based on our present results, although the number of patients included in this study was small, we consider that only the intervention, including telephone interview, but also the initiation of opioid led to the decrease of pain, for which pharmacists’ intervention is necessary.

There are a few limitations to the present study. The data were limited to those produced by prospective observational studies and were generated during routine pharmaceutical care for patients with cancer. Therefore, for ethical reasons, we were unable to make comparisons with a no-treatment control group. Moreover, the present cohort 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. This study limitation reflects the unfamiliarity of physicians and medical staffs with the concept of pharmacist interventions or consultations; further studies having wider acceptance of pharmacist contributions to QOL are needed.

CONCLUSION

In this study, we showed that pain and side effect management can be appropriately achieved by pharmacist interventions through continuous interviews and assessments of patients with cancer before consultations with physicians, thus highlighting the importance of pharmacist interventions.

Acknowledgment This work was partly supported by KAKENHI and a Grant-in-Aid for Scientific Research (C) (No. 16K08891) from the Japan Society for the Promotion of Science.

Conflict of Interest The authors declare no conflict of interest.

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