

Original Article

## Physician's Attitude toward Treating Breakthrough Cancer Pain in Korea

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**Purpose:** Adequate control of breakthrough pain is essential for patients with cancer. Managing breakthrough pain mainly depends on understanding the concept of breakthrough pain and the proper usage of rescue medication by physicians. This study aims to assess the attitudes and practice patterns of palliative physicians in managing breakthrough pain for patients in Korea. **Methods:** This study was based on data from the 2014 breakthrough cancer pain survey conducted by the Korean Society for Hospice and Palliative Care. One hundred physicians participated in the online survey. Among total 33 self-reported questionnaires, twelve items were selected in this analysis. **Results:** Rapid onset of action is the main influencing factor in selecting rescue opioids. Oral oxycodone (65%) and parenteral morphine (27%) are commonly used. A few physicians (3%) prefer to use transmucosal fentanyl. The percentage of physicians prescribing oral oxycodone due to its rapid onset of action is just 21.5%, whereas the percentage of physicians using parenteral morphine is 81.5%. Two thirds of respondents (66%) answered that breakthrough pain is not well controlled with rescue medications. **Conclusion:** There is a gap between the needs of physicians in terms of the perceived difficulties of managing breakthrough cancer pain and their practice patterns selecting rescue medications.

**Key Words:** Breakthrough pain, Palliative care, Opioid analgesics

### INTRODUCTION

Breakthrough cancer pain (BTcP) has been defined as “a transient exacerbation of pain that occurs either spontaneously

or in relation to a specific and predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain” (1). The prevalence of BTcP varies with clinical settings and definitions of BTcP, ranging from 39.9% in outpatient clinics to 80.5% in hospice settings (2). The

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occurrence of breakthrough pain has been reported to interfere with daily living, to decrease personal relationships and to increase psychological distress, thereby resulting in a poor quality of life among cancer patients (3). In addition, cancer patients with BTcP are known to require higher costs (\$12,000/year) for hospitalization, emergency department visits, and physician office visits than non-BTcP patients (\$2,400/year) (4).

Despite ongoing improvement of guidelines for pain control in cancer patients and the development of effective analgesics, BTcP is still considered difficult to manage (5). There are a number of barriers against properly managing BTcP. A growing body of literature has documented that a fear of opioid addiction and tolerance among patients, inadequate knowledge and assessment of pain by physicians, and negative public attitudes may be barriers to the proper management of cancer pain (6,7). Among many treatment modalities, including correction of the underlying cause, avoiding precipitating factors, usage of rescue medication, and non-pharmacologic interventions, appropriate usage of rescue medication is most important (8). Traditionally, oral immediate-release opioids such as morphine and other relevant opioid analgesics such as oxycodone and hydromorphone have been prescribed as rescue medications (9). Some researchers have demonstrated, however, that traditional rescue medications may not match the temporal characteristics of BTcP (10,11). Most episodes of BTcP are characterized by patients reaching peak pain intensity within 10 minutes, followed by the disappearance of untreated pain within 60 minutes (12). Inconsistent with this presentation, almost all immediate-release preparations are known in pharmacokinetic studies to have delayed onset for producing peak analgesia (>one hour) and long durations of efficacy (3~6 hours) (13). Therefore, a mismatch between temporal characteristics of BTcP and the mechanisms of rescue medications may result in suboptimal pain management and undesirable adverse effects for patients, such as sedation, confusion, and fatigue (14). Recent research in other countries has shown that many physicians still use conventional rescue medications despite the availability of more appropriate opioids (15,16). However, there is little data regarding the management of BTcP among Korean physicians. The aim of this study is to assess the practice patterns of hospice-palliative physicians concerning BTcP and its treatment,

especially in terms of drugs of choice, the reasoning for these preferences, and physician perceptions of what is needed to best manage breakthrough cancer pain when it comes to rescue medications.

## METHODS

### 1. Study design, participants and procedures

The 2014 breakthrough cancer pain survey conducted by the Korean Society for Hospice and Palliative Care (KSHPC) was analyzed. This survey was conducted in order to understand physician perceptions about breakthrough cancer pain and the pain management practice patterns of physicians. Prior to the study, KSHPC recruited a working group. Nine members comprised this group, including four family physicians, three medical oncologists, one radiation oncologist, and one medical statistician. Among members of the KSHPC, medical specialists with regular membership and who are managing cancer pain with opioid analgesics in over 10 cases per month were eligible for participation. The KSHPC sent emails with the address of the online survey to a total of 382 members, encouraging participation from September to December of 2014, until a total of 100 members completed and submitted the survey. After completion of the questionnaire, participants received a reward for their participation. This study was approved by the Institutional Review Board of the Yonsei University College of Medicine in Seoul, Korea (IRB no. 4-2015-0346). Because this study analyzed existing survey data, the exemption of the informed consent requirement was determined by the IRB committee.

### 2. Questionnaire

The questionnaire was specifically developed for the aims of the survey by the working group of the KSHPC in accordance with clinical experience and a review of existing literature. After several face-to-face meetings and contact via email, 33 questions, including seven items addressing background characteristics such as physician's age, sex, years of practice, and workplace, were selected for inclusion in the final survey questionnaire. The instrument also contained questions on knowledge of cancer management, barriers to managing cancer pain, capacity for pain assessment (including severity, frequency and duration of pain), physician level of education

on drug usage, treatment of BTcP with physician reasoning for selecting each drug, important factors in selecting drugs, and perceived difficulties in managing breakthrough cancer pain. The physicians were also asked how many patients with cancer they saw in a month, and whether or not they prescribe opioid analgesics for cancer pain. Respondents who saw at least 10 cancer patients in a month and answered yes to the question of prescribing opioid analgesics for pain were included in this survey. To focus on physician practice patterns concerning BTcP, this paper presents findings on important factors in physician selection of short-acting opioids, drugs of choice with reasoning, and perceived difficulties of pain management among physicians.

### 3. Statistical analysis

Characteristics of the respondents were summarized as mean (SD) or number of subjects (percentage), as appropriate. The Mann-Whitney's U test was used to examine the difference of clinical characteristics between general and palliative wards. A two-sided P value less than 0.05 was considered as the minimum level of statistical significance. All statistical analyses was performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

## RESULTS

One hundred clinical physicians participated in the 2014 breakthrough cancer pain survey were analyzed. The mean age of participants was 46.1 years, and the majority of participants were male (55%). The participants belonged to 10 clinical departments: 53% were from the department of medical oncology, 30% were from family medicine, and 17% of participants were from other departments. Half of the clinicians (50%) worked in the general ward, while 38% of clinicians worked in the palliative care ward. In all, 45% of clinicians had 10 or fewer years of practice, and the average number of years of practices was 14.2 years. One third of participants (36%) saw fewer than 30 cancer patients in a month, while 27% and 24% of participants saw 31~50 patients and 51~100 patients, respectively (Table 1).

Data regarding the drugs of choice for the management of all cancer pain and BTcP are shown in Figure 1. Oxycodone was the most commonly prescribed opioid for all cancer pain

(59%), and immediate-release oxycodone was also frequently used for BTcP (65%). Almost all the clinicians that used morphine for BTcP preferred parenteral access (27%) rather than oral administration (1%) of the drug. The percentage of clinicians selecting transmucosal fentanyl to manage BTcP was low (3%). Among reasons for selecting immediate-release oxycodone to control BTcP, the top two reasons included ease of administering the drug (35.4%) and having a lot of prescription experience with the drug (27.7%). On the other hand, most physicians (81.5%) answered that the reason for prescribing parenteral morphine was due to its rapid onset of action (Table 2). Findings on physician cognition of charac-

Table 1. Characteristics of Respondents (N=100).

Characteristics	N
Sex	
Male	55
Female	45
Age (yr)	
31~40	37
41~50	31
≥51	32
Department	
Medical oncology	53
Family medicine	30
Anesthesiology	5
Internal medicine, other	3
Surgery	3
Radiation oncology	2
Gynecology	1
Emergency medicine	1
Urology	1
Pediatrics	1
Workplace	
General ward	50
Palliative care ward	38
Only outpatient clinic	8
Long-term care facility	4
Years of practice as specialist	
≤10	45
11~20	29
21~30	21
≥31	5
Average number of cancer patients seen in a month	
≤30	36
31~50	27
51~100	24
101~200	6
≥201	7

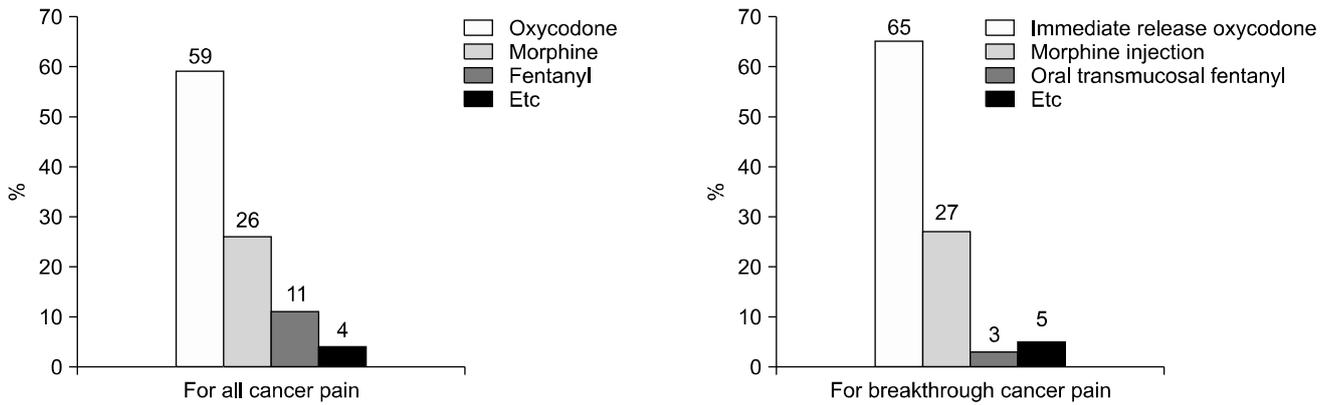


Figure 1. Drugs of choice for managing all cancer pain and breakthrough cancer pain.

Table 2. Reason for Selecting Preferred Short-Acting Opioid.

Categories	Oral oxycodone (N=65)	Parenteral morphine (N=27)
	N (%)	N (%)
Easy to administer	23 (35.4%)	0 (0%)
A lot of prescription experience	18 (27.7%)	1 (3.7%)
Rapid onset of action	14 (21.5%)	22 (81.5%)
Easy to titrate	7 (10.8%)	3 (11.1%)
Strong efficacy	1 (1.5%)	0 (0%)
Less adverse events	1 (1.5%)	0 (0%)
Other comment	1 (1.5%)	1 (3.7%)

Other comment: There is no other medicine to prescribe (N=1).

teristics of each short-acting opioid, including oral oxycodone, parenteral morphine, and oral transmucosal fentanyl revealed that each drug has different characteristics. Ninety-seven of the responding clinicians had experience with prescribing oral oxycodone. Collectively, the clinicians had a lot of prescription experience (95%) and thought that oral oxycodone is easy to administer (84%). However, only 47% of the physicians with experience in prescribing oral oxycodone agreed that it has rapid onset of action. In the case of parenteral morphine, 98% and 95% of 94 clinicians characterized it as having rapid onset of action and strong efficacy, respectively. Similar to their experience with oral oxycodone, most of the physicians had sufficient experience in prescribing parenteral morphine (96%). Only 34% of 80 physicians had a lot of experience in prescribing oral transmucosal fentanyl, despite 70% and 78% characterizing the drug as fast acting and easy to administer, respectively.

Influencing factors on the prescription of short-acting opioids

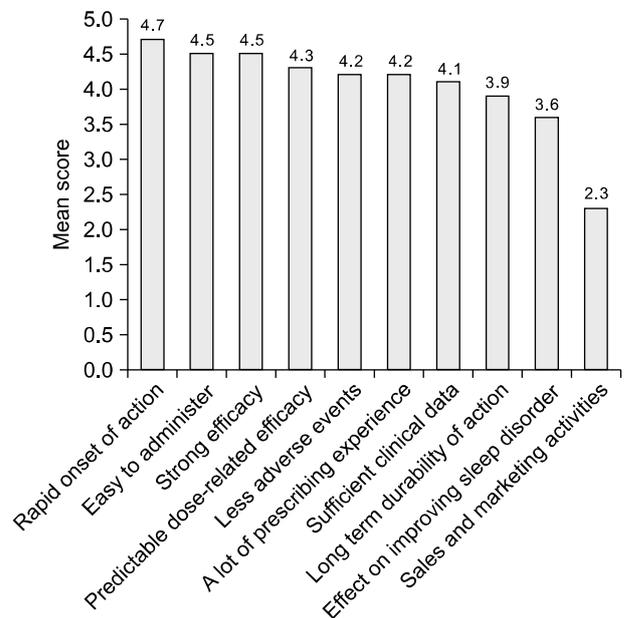


Figure 2. Influencing factors for prescribing short-acting opioid for breakthrough cancer pain.

for BTcP are shown in Figure 2. Rapid onset of action is the most important influencing factor in the selection of rescue medications by physicians (mean score=4.7). Among the top three factors, the remaining two factors are ease of administering and strong efficacy of the medications. In the section on difficulties in managing BTcP, the majority of clinicians (66%) answered that pain is not well controlled for patients, despite the use of rescue medications. In contrast, the economic burden of high prices for medications was not considered as a difficulty (Table 3).

**Table 3.** Difficulties in Managing Breakthrough Cancer Pain (N=100).

Categories	N
Pain is not well controlled with rescue medications.	66
Worries about adverse effects such as respiratory depression and delirium.	11
There are not proper opioids for breakthrough pain.	10
High prices of short-acting opioids are burdensome.	7
Other comments	6

Other comments: There is no difficulty in managing breakthrough cancer pain (N=2), It is difficult to manage breakthrough cancer pain with medications that have short durations of efficacy (N=1), Patients do not want to take short-acting opioids, despite education about their usefulness (N=1), It is difficult to rapidly administer short-acting opioids (N=1), Incident breakthrough pain, including moving and urination, is difficult to manage (N=1).

## DISCUSSION

The present study demonstrates that there is a gap between the needs of physicians in terms of their perceptions about the difficulties of managing breakthrough cancer pain and their selection of rescue medications. Many physicians assert that rapid onset of action is the most important influencing factor in prescribing short-acting opioids, whereas two thirds of physicians have used immediate-release oxycodone rather than parenteral morphine and oral transmucosal fentanyl in clinical practice. Interestingly, among physicians with experience in prescribing oral oxycodone, just one half of physicians agreed on its rapid onset of action. In addition, oral transmucosal fentanyl, which is known to have faster effects, was selected as the rescue medication of choice by only a small percentage of respondents. Comparing these findings with the findings of other studies, physicians in palliative care institutions in Italy commonly prescribe oral morphine to manage breakthrough cancer pain, and also use other access routes for medications, including subcutaneous and intravenous access routes. In contrast, Korean physicians prefer oral oxycodone (15). In the case of selecting morphine as a preferred rescue medication, most respondent use the parenteral access route rather than the oral route. We consider the cause of this preference for parenteral morphine to be due to differences in workplaces. Subgroup analysis according to workplace demonstrates that usage of parenteral morphine is significantly higher in palliative wards ( $P < 0.001$ ).

In Korea, patients with advanced cancer stay in the hospi-

tal for a mean of  $20.2 \pm 21.2$  days per admission in the palliative ward. More than 70% of these patients face death in the hospital (17). More specifically, most patients in the palliative ward are in the process of dying, which is related to a higher prevalence of dysphagia and dry mouth (18,19). We assume that these statistics partly explain why physicians in palliative wards have little choice but to commonly prescribe parenteral morphine.

Fentanyl is a potent synthetic opioid with highly lipophilic characteristics. It is rapidly absorbed via mucosal membranes and diffuses across the blood-brain barrier, resulting in the rapid onset of effects (20). A variety of researchers have suggested that transmucosal fentanyl preparations might be a better fit in managing BTcP than oral opioids, because transmucosal fentanyl has characteristics of short duration and high potency in addition to rapid pain response (11,21). Nevertheless, few physicians have prescribed transmucosal fentanyl in Korea. In a European survey of 1,000 oncologic patients, 19.1% of participants answered that they had been prescribed fentanyl for BTcP (6). Another survey demonstrates that 42.1% and 16.2% of physicians in 12 European countries normally use oral transmucosal fentanyl and intranasal fentanyl, respectively (22). In an Italian survey, 21 of 118 physicians at dedicated palliative care institutions select fentanyl alone or fentanyl with other opioids as their drug of choice for controlling BTcP (15). On the other hand, the percentage of Canadian patients with BTcP who had been prescribed fentanyl was only 2.9% (16). Based on comparison with the physician surveys of other countries, transmucosal fentanyl is used more frequently in Korea than in Canada, but less frequently than in European countries. We assume that prescriptions with characteristics that are unsuitable for BTcP might be linked to the perceptions of physicians regarding the difficulties of managing BTcP, despite the widespread use of rescue medications.

There may be several reasons for differences in prescribing opioid analgesics in managing BTcP, especially in the case of transmucosal fentanyl, which is known for more effective analgesic results.

First, the knowledge of a physician impacts resulting prescriptions. A number of studies have demonstrated the association between the knowledge of a medical staff and the management of cancer pain (23,24). A lot of medical

members rely on specific guidelines in clinical practice. Looking into current guidelines in Korea, Canada, and Europe, there are some differences in protocol among the countries. European guidelines recommend transmucosal fentanyl as an additional option for managing BTcP, and indeed, as the preferable option in some cases (25). On the other hand, Canadian guidelines do not include any information about transmucosal fentanyl (26). This lack of information may be due to the fact that fentanyl preparations have only recently become available in Canada (27). Korean guidelines for cancer pain management were first published in 2004, and are now available in the 6th edition, updated in 2015 (28). Even though some improvements in cancer pain management have been achieved with these updated guidelines, there is still insufficient information to properly define and manage BTcP using appropriate analgesics (29). In addition, in a Korean survey of physician knowledge about cancer pain guidelines, more than 40% of physicians answered incorrectly on items related to BTcP (23). Accordingly, further updated guidelines based on current data about BTcP, together with continuing education for physicians, is warranted to improve the management of breakthrough pain for cancer patients.

Second, higher costs might impact physician hesitance to prescribe newly-developed medication formulations in practice, even though a few physicians answered that they felt difficulties to manage breakthrough cancer pain due to high prices. Economic restrictions are suggested as a barrier in prescribing rapid-acting opioids in previous research (15). In fact, the cost of fentanyl preparations is several times higher than the cost of traditional opioids in Korea.

Third, some physicians might be reluctant to prescribe recently developed formulations due to lack of experiences of prescription in clinical practice. Song et al. reported that Korean physicians considered the private experience including prescription experience as the most important factor among several prescription criteria (30). An oral transmucosal fentanyl has been available in many countries since the 1990s. However, buccal fentanyl preparation was first available in 2008 and other formulation of fentanyl became available in Korea in 2014. Thus, there is not enough time to experience characteristics of newly developed formulation in clinical practice, resulting in gap between discrepancy and practice. The use of opioid analgesics is under strict regulation in

Korea. The difficulties of opioids storage and administration in hospital, especially small hospital, also important factor to limit physicians' experience on prescribing opioids analgesics. The optimal balance in regulatory policy will ensure effective management of cancer pain and protect patients against misuse of opioids.

This study has some limitations. First, the participants may not be representative of all palliative care physicians. Almost all the respondents were medical oncologists and practitioners of family medicine. In addition, the number of physicians who participated in this study is relatively low. If more physicians from other specialties had been included in this study, then the results may have been different. Second, all the participating physicians herein are members of the KSHPC, and therefore are highly dedicated to their work. This probably overestimates the results relative to the actual practice patterns of physicians involved in the pain management of cancer patients. Third, there may be discrepancies between the responses of participants about what they would do in theory and what they actually do in their workplaces on a daily basis in dynamic circumstances. Despite these limitations, we believe that the present study is the first to assess the gap between the needs of cancer patients and the actual patterns of rescue medication prescription among palliative physicians in Korea.

In conclusion, our data suggest that there is a difference between the needs of physicians in terms of their perceptions about the difficulties of managing breakthrough cancer pain in patients and the actual patterns of prescription among palliative physicians in Korea. The responding physicians felt that management of BTcP is difficult. This indicates the need for further studies on BTcP related barriers in Korea. We suggest that additional researches should focus on more physicians treating cancer pain to identify a true picture of the physicians' attitude on BTcP. Moreover, updated guidelines, the continuing education of physicians, and support from government are required to meet patient needs and thereby achieve optimal treatment of BTcP.

## 요 약

**목적:** 돌발성 통증을 적절히 조절하는 것은 암환자에서 필수적이다. 돌발성 통증을 조절하는 것은 의료진이 돌발성 통증에 대해 잘 이해하고 적절한 구제 진통제를

사용하는 것에 달려있다. 본 연구는 한국 완화의료 전문의들의 돌발성 통증에 대한 견해와 진료 형태에 대해 알아보고자 하였다.

**방법:** 본 연구는 한국호스피스 완화의료학회에서 시행된 2014년 돌발성 통증 설문조사를 바탕으로 진행하였다. 100명의 의사가 온라인 설문조사에 참여하였다. 총 33개의 자가 기입식 설문 문항 중에서 12개의 항목이 분석에 사용되었다.

**결과:** 빠른 작용 발현은 구제 진통제를 선택함에 있어 가장 중요한 요소였다. 경구 옥시코돈(65%)과 모르핀 주사제(27%)는 흔히 사용되는 구제진통제였다. 소수의 의사들(3%)만이 점막 흡수형 펜타닐을 선호하였다. 빠른 작용 발현 때문에 경구 옥시코돈을 선택한다고 답변한 의사들은 21.5%였으며, 반면에 빠른 작용 발현 때문에 모르핀 주사제를 처방한 의사들은 81.5%였다. 전체 응답자의 약 66%는 돌발성 통증이 구제 진통제로 잘 조절되지 않는다고 답변했다.

**결론:** 돌발성 통증 조절에 의료진들은 어려움을 느끼고 있었고, 의료진들이 구제진통제를 선택함에 있어서 필요로 하는 중요한 요소와 실제 처방의 형태에는 차이가 있었다.

**중심단어:** 돌발성 통증, 완화의료, 마약성 진통제

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