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We Might Need More Education for Breakthrough Cancer Pain: The Pilot Survey among Korean Medical Oncologist

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Abstract

Introduction: Breakthrough cancer pain (BTcP) has been reported to occur in more than half of cancer patients. However, despite the introduction of various treatment options, BTcP remains under-diagnosed and under-treated. Because physicians' knowledge and attitudes are related to adequate BTcP management, it is important to explore physicians' knowledge, attitude and clinical practice in managing BTcP.

Objectives: Purpose of this study is to evaluate medical oncologist's knowledge, attitudes and clinical practice in BTcP management.

Method: We randomly contacted with a medical oncologist (MO) who has been experience more than five years in the field of oncology and conducted a survey.

Results: 30% (50/165) of contacted medical oncologists responded the survey. Median age was 46 years old (range, 35-65) and 70% (35/50) was male. The median knowledge score of BTcP was 7 (range, 2-10) and it was significantly lower than that of general cancer pain (median 9, range 4-10) (p = <0.001). In the assessment of attitudes, 54% (27/50) of respondents replied to assess cancer pain only when the patient complained of pain and 44% (22/50) of respondents don't evaluate the cancer pain in detail including breakthrough cancer pain. In the survey of drug preference, oxycodone was most frequently prescribed opioid for the background pain and BTcP. Considerable number of respondents (34%, 17/50) answered that they use transmucosal fentanyl in opioid dose titration.

Conclusion: The knowledge score of BTcP was significantly lower than that of general cancer pain in medical oncologists and a lack of understanding of BTcP led to inadequate management of BTcP.

Introduction

Pain is one of the most common symptoms associated with cancer, and about 60% of cancer patients experience cancer pain during their illness [1]. Cancer pain is categorized by its nature and divided into two types: background pain and breakthrough pain. Breakthrough cancer pain (BTcP) was first identified in 1990 [2], and for decades, various definitions of BTcP have been proposed to differentiate BTcP from other types of pain. In recent years, the definition proposed by Davies et al. [3] has been widely accepted

and is described as follows: "a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain." To control BTcP, short acting opioids are usually recommended as rescue doses by guidelines [4-6]. Traditional short acting opioids, however, have limitations in their pharmacokinetic/pharmacodynamic profiles to control BTcP, which is characterized by short time to peak intensity (10 minutes), short duration (less than 60 mintues), and relatively high intensity [7].

Recently, fentanyl formulations with various delivery routes have been developed and are considered to be proper analgesics in the management of BTcP. Indeed, there are data showing that buccal fentanyl is effective in treatment of BTcP [8-10] and multiple randomized trials suggest that sublingual and nasal transmucosal formulations of fentanyl are also effective in managing BTcP [11,12]. With these results, rapid onset opioids are considered as optimal rescue medication for BTcP among experts. Despite the introduction of various treatment options, BTcP remains under-diagnosed and under-treated. Recent survey of 573 European cancer patients revealed that BTcP was occurred in 63% of cancer patients and only one third of these patients received adequate pain management [13]. One of the major barriers to optimal care for cancer pain is physicians' misunderstanding and lack of knowledge of pain [14] and recent study has reported that there is a significant association between the level of physicians' knowledge and proper pain management [15].

Unsurprisingly, uncontrolled BTcP affects patients' activity, motivation, and overall quality of life [16]. Improperly relieved BTcP also increases the level of anxiety and makes patients be dissatisfied with their overall pain management [17]. Because physicians' knowledge and attitudes are related to adequate BTcP management, it is important to explore physicians' knowledge, attitude and clinical practice in managing BTcP.

In Korea, two thirds of physician who do palliative care in the cancer centers are medical oncology specialists [18]. Therefore, we carried out a survey among medical oncologists to explore physicians' knowledge and attitudes, and clinical practice in BTcP management.

Materials and Methods

Procedures

During the month of May 2016, medical oncologists who are registered in Korean Cancer Study Group (KCSG) were randomly contacted by telephone call with an introduction of a survey. Survey paper was distributed to only whom agreed the survey by interviewee. Eligibility includes more than 5 years of experience in the field of oncology and prescribe opioids for more than 20 patients per months. This study was approved by institutional review board.

Survey Instruments

The survey instrument was developed with referenced to previous research by three investigators (JH Kwon, SK Baek, and MA Lee) and review and feedback were performed among the investigators [15,19-21]. Finally, sixteen questionnaires and one vignette were selected and tested among investigators. Each questionnaire has its own specific objectives and can be grouped into broad categories: assessment of knowledge, attitudes and clinical practice of medical oncologists in the management of cancer pain. To evaluate medical oncologists' knowledge of BTcP management, true or false questionnaires were used. Two kinds of true or false questionnaire was developed based on the NCCN adult cancer pain guidelines (ver.1.2016) and each included 10 questions. Two questionnaires asked participants about general cancer pain and BTcP. respectively. Scoring from 0 to 10 was used to assess medical oncologists' knowledge of cancer pain management. To evaluate medical oncologists' attitudes and their compliance to the cancer pain management guidelines, three questionnaires and one case vignette were used.

These questionnaires were focused on the patient selection for cancer pain assessment, the way how to assess cancer pain, follow up duration after initiation of opioid for cancer pain. A case vignette was presented at the last part of the survey which has two step clinical scenarios. First step is a clinical situation of uncontrolled background pain and second step is a situation for uncontrolled BTcP after controlling background pain. Proper pain management was asked for each step and the type of BTcP was asked for the second step. Additionally, we asked eleven questionnaires to identify their preferences in the management of BTcP in clinical practice. Participants are asked to choose the most preferred opioid for background cancer pain and BTcP. We also asked about individual treatment tendencies for BTcP and their thoughts for ideal characteristics of opioids adequate for BTcP management.

Statistical Analysis

We used Mann-Whitney U test to compare median values and Chi-squared tests to compare percentages between different groups. All significance levels refer to two-sided tests. A P-value of less than 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS, Chicago, IL) version 21.0.

Discussion

In the current study, we conducted the survey and evaluated medical oncologists' knowledge, attitudes and clinical practice in the management of BTcP. This study showed that knowledge scores of BTcP was significantly lower than that of general cancer pain. We also identified that a lack of understanding of BTcP might lead to inadequate management of BTcP. In the BTcP knowledge assessment, respondents had difficulty with questions about the definition of BTcP and particularly lacked understanding of the background pain conditions to define BTcP. BTcP is a relatively new concept and it has been less than 30 years since the first effort to identify and define BTcP in 1990. Until now, there is no unanimous consensus on the clinical features to define BTcP despite an international effort to achieve consensus. Considering this situation, BTcP may still be an unfamiliar concept for physicians, even for oncology specialists in Korea. There are ongoing debates

on criteria for severity or duration of BTcP and how to define 'well-controlled background pain' [7,22-25]. Consensus on these debates will lead to the improvement of knowledge for BTcP and until then, a comprehensive multidisciplinary approach is needed to diagnose and manage the BTcP appropriately.

Lack of understanding of BTcP has related to inadequate BTcP management. Half of respondents replied that they don't ask patients about cancer pain in detail including BTcP and they only assess cancer pain when the patient complained of pain. Questionnaires and case vignette also revealed that considerable number of medical oncologist misuse transmucosal fentanyl during opioid titration. This is an unexpected outcome and may raise an important clinical issue related to the usage of transmucosal fentanyl in BTcP. Transmucosal fentanyl is considered the ideal analgesic for BTcP management and, in this survey, medical oncologists also responded that they prefer rapid onset opioids compared to parenteral or short acting opioids, significantly. However, since the equivalence dose of morphine to transmucosal fentanyl is not established, the usage of transmucosal fentanyl is limited to the management of BTcP and should not be used in the opioid dose titration for background pain. Indiscriminate use of transmucosal fentanyl in opioid dose titration can result in opioid abuse which can lead to aberrant behaviors with opioid and chemical coping.

In the retrospective analysis of 1,160 chronic pain patients receiving transmucosal fentanyl [26], the incidence of drug abuse events (1%) and aberrant drug-related behaviors (11%) were reported to be relatively low. However, opioid abuse events related to transmucosal fentanyl might have been underestimated because this report included patients from controlled clinical studies and over the past decade, the amount of transmucosal fentanyl prescription has increased significantly. There has no risk evaluation and mitigation strategies for opioids in Korea, therefore every physician has allow to prescribe any opioids including transmucosal fentanyl for cancer patients within the insurance guidance [27]. Given our worrying outcomes, thorough education for the diagnosis and management of BTcP is strongly recommended to prepare for the risk of opioid abuse in the future. 17 respondents (34%) replied that they use transmucosal fentanyl when titrating opioid in clinical practice and 14 respondents (28%) answered to the case vignette part 1 that they will use transmucosal fentanyl for opioid dose titration. However, the response to the knowledge questionnaire was not related to the choice for the case vignette in using transmucosal fentanyl for titration.

This might be a limitation of using case vignette to test the knowledge in the clinical practice. Current study has potential limitations. First, low contact number of oncologists and low response rate has some limitation to represent medical oncology societies of Korea. Second, Because the survey did not include the patients' medical records regarding pain control the result might not reflect real knowledge of medical oncologist in Korea. We also could not find the relation between knowledge and clinical practice. In this survey, we found that some medical oncologists in Korea are unfamiliar with the definition of BTcP and they misuse transmucosal fentanyl in the opioid dose titration. Despite its advantages, transmucosal fentanyl is a double-edged sword which can cause opioid abuse and special warning and education is recommended. Further studies to find the factors related to inadequate knowledge of background pain among physicians and also need to conduct survey with large population reflecting knowledge, attitudes and clinical practice of BTcP management among physicians in Korea.

Result

Characteristics of Survey Respondents

Table 1 demonstrates the characteristics of respondents. About 39% (165/425) of medical oncologists registered in KCSG were randomly contacted and 30% (50/165) of them were responded the survey. Median age was 46 years old (range, 35-65) and 70% (35/50) was male. Median duration of their career as a medical oncologist was 15 years (range, 6-30) and median number of patients who received opioid prescription during last 1 month before the survey per each medical oncologist was 100 (range, 25-500).

Table 1: Characteristics of participants.

Characteristics	Number of Respondents (%)
	Total n=50
Age (median)	46 (range 35-65)
Sex	
Men	35 (70%)
Women	15 (30%)
Year of experience as oncology specialist*	
6-10 years	12 (25%)
11-15 years	14 (30%)
16-20 years	16 (34%)
21-25 years	5 (11%)
Number of cancer pain patients prescribed opioids (recent 1 month)	
<19 patients	0 (0%)
20-39 patients	4 (8%)
40-59 patients	11 (22%)
60-79 patients	2 (4%)
80-99 patients	1 (2%)
≥100 patients	32 (64%)

Note: * n=47.

Knowledge of Cancer Pain

The 10 true or false questions and responses are listed in Table 2. Median knowledge score of general cancer pain management was 9 (range, 4-10). For most questions, correct answer rate was as

high as > 80%. However, the correct answer rate to question about how to stop opioid in patients with resolved pain (Question I) was relatively low (74%). For questions related to BTcP, the median knowledge score was 7 (range, 2-10), and the score was significantly lower than that of questions about general cancer pain (median = 9, range, 4-10; p = <0.001). Particularly, respondents had difficulty with questions about the definition of adequately controlled background pain to define BTcP (Question C, G) with 22-42% of correct answer rate. We compared knowledge scores between groups stratified by duration of career (>10 vs. ≤10 years) and number of patients receiving patients (>100 vs. ≤100 patients/ month) and there was no statistically significant difference between groups.

Table 2: Medical oncologists' knowledge and attitude of cancer pain (n=50).

Statement	True n (%)	False n (%)	Don't know n (%)
1. Participants' responses about general cancer pain management			
A. Most cancer pain can be controlled by medication	44 (88%)	6 (12%)	0 (0%)
B. The pain control succeeds only when the pain scale becomes zero	9 (18%)	41 (82%)	0 (0%)
C. The pain control succeeds when the patient's individual pain control goal is achieved	43 (86%)	7 (14%)	0 (0%)
D. Opioids used in cancer patients can easily cause addiction	5 (10%)	45 (90%)	0 (0%)
E. Opioids compromise patient's immunity	11 (22%)	39 (78%)	0 (0%)
F. Moderate to severe cancer pain should be controlled with long-acting opioids	45 (90%)	5 (10%)	0 (0%)
G. Opioids do not have ceiling effects and the dose can be increased without an upper limit	43 (86%)	7 (14%)	0 (0%)
H. Constipation caused by opioids should be prevented from the beginning of opioids prescription	39 (78%)	11 (22%)	0 (0%)
I. If the cause of the pain is resolved, opioids should be discontinued immediately regardless of current dose	13 (26%)	37 (74%)	0 (0%)
J. If opioids are used from the beginning of cancer pain control, opioids may be less effective, even with increased dose	8 (16%)	41 (82%)	1 (2%)
2. Participants' responses about breakthrough cancer pain (BTcP) management			
A. BTcP refers to a temporary deterioration of pain in patient with well-controlled background cancer pain	49 (98%)	0 (0%)	1 (2%)
B. In patient who has NRS 6 background cancer pain, NRS* 10 pain occurring 6 times a day can be recognized as a BTcP	22 (44%)	27 (54%)	1 (2%)
C. In patient without opioids, deterioration of pain 2-3 times a day can be recognized as a BTcP	26 (52%)	21 (42%)	3 (6%)
D. Pain caused by certain movements or postures in a patient with well-controlled background pain is not a BTcP	12 (24%)	37 (74%)	1 (2%)
E. BTcP can occur spontaneously or can be caused by certain movements or postures	48 (96%)	2 (4%)	0 (0%)
F. Pain which occurs at the end of a dosing interval in a patient with well-controlled background pain is a BTcP	9 (18%)	40 (80%)	1 (2%)
G. Even if patient has moderate to severe background cancer pain (NSR ≥4), it can be recognized as BTcP if pain aggravates distinctively	38 (76%)	11 (22%)	1 (2%)
H. BTcP should be managed separately from background cancer pain	39 (78%)	11 (22%)	0 (0%)
I. Pain which occurs during opioid dose adjustment for background cancer pain is BTcP	23 (46%)	26 (52%)	1 (2%)
J. Duration of BTcP is usually less than 60 minutes	39 (78%)	9 (18%)	2 (4%)

Note: * NRS=numeric rating scale.

Attitudes and Compliance with The Cancer Pain Management Guidelines

We asked 3 questionnaires and 1 case vignette to assess medical oncologists' attitudes and their compliance with cancer pain management guidelines. Twenty-seven respondents (54%) were assess cancer pain only when the patient complained of pain. Only 56% (28/50) of respondents evaluated the pain in detail including breakthrough cancer pain and 26% (13/50) of respondents answered that they only checked for the presence of pain (Table 3). Most of respondent followed up their patients in 2 weeks after initiating opioid analgesics for pain control (88%, 44/50) (Table 3).

Table 3: Clinical practice of breakthrough cancer pain management (select 1).

Questions	Number of choices (%)
1. When you ask about cancer pain You_____	
A. Briefly ask whether patients have pain or not, and check whether current medicine is effective	13 (26%)
B. Just check patients' pain score	5 (10%)
C. Just ask patients' average and maximum pain score	3 (6%)
D. Ask patients' average pain score, maximum pain score and BTcP in detail	28 (56%)
E. Often omit pain assessment because you are too busy	1 (2%)
2. Select your first follow-up period after initiating opioids for the management of cancer pain	
A. 1-2 days after initiating the treatment	12 (24%)
B. 3-6 days after initiating the treatment	10 (20%)
C. 1 week (7-13 days) after initiating the treatment	22 (44%)
D. ≥ 2 weeks (≥ 14 days) after initiating the treatment	5 (10%)
E. Next patient visit	1 (2%)

Note: BTcP=breakthrough cancer pain.

BTcP Characteristics, Its Value and Implementation in Clinical Practice

Most characteristics of BTcP in the survey were considered important more than score 6 on a Likert scale (1 unimportant, 7 very important) (Table 4). More than 70% of respondents replied that they always ask location of pain, current prescribed opioids, and its efficacy when evaluating BTcP (Table 4). Respondents agreed that short action time less than 15 minutes, the maximum duration of action less than 2 hours, trans-mucosal route of administration are the ideal characteristics for BTcP medication (Table 5). Of the three different opioid formulations in the management of BTcP, respondents preferred rapid onset opioid to parenteral and short acting opioids and there was statistical significance (p = <0.001) (Table 5). 88% (44/50) of respondent also replied that they titrate the dose of opioids according to the intensity of BTcP. They referred to the number of BTcP episodes/day as the most important factor when titrating the opioid dose (Table 5) and many of them responded that they would follow up patient in 3-7 days after the initiation of the first BTcP medication (36%, 18/50) (Table 5).

Table 4: Characteristics of BTcP, its importance and clinical practice among medical oncologist (n=50).

Questions	Importance score, median (Q1~Q3)[1)]	Ask to patients			
		Never (%)	Rarely (%)	Sometimes (%)	Always (%)
Current prescribed opioids	7 (6-6)	2	8	16	74
Location of pain	6 (6-6)	0	2	22	76
Number of flares per day and/or week	6 (6-6)	0	6	46	48
Efficacy of current opioids	7 (6.75-7)	0	2	26	72
Intensity of flares (VAS or NRS)	6 (6-6)	2	6	48	44
Adherence to opioids	6 (6-6)	0	4	46	50
Spontaneous or triggered occurrence of pain	6 (5-5)	0	10	50	40
Radiating pain	6 (4.75-5)	2	24	52	22
Duration of each flare	6 (5-5)	0	8	44	48
Impact of flare on night-sleep	6 (6-6)	0	8	50	42
Time to peak intensity	6 (5-5)	2	26	56	16
Similarity of etiology between BTcP and background pain	6 (5-5)	2	18	64	16

Note: 1) ranged from 1 (unimportant) to 7 (very important), BTcP, breakthrough cancer pain.

Table 5: Medical oncologists' preference in the management of BTcP. Items were scored from 1 (unimportant or strongly disagree) to 7 (very important or strongly agree) {Citation}.

Questions		Median (Q1-Q3)
1. The characteristics of the ideal opioid to manage BTcP		
A. Onset time	Less than 15 min	7 (7-7)
	Less than 30 min	5 (4-4)
B. Duration of action	4 to 5 hours	5 (4-4)
	1 to 2 hours	6 (5-5)
C. Route of administration	Oral (swallowed)	5 (4-4)
	Trans-mucosal (oral)	6 (6-6)
	Trans-mucosal (nasal)	5 (5-5)
	Subcutaneous	4 (3-3)
	Intravenous	4 (2-2)
2. Do you agree with following sentence (1 strongly disagree – 7 strongly agree)?		
A. Rapid onset opioids are the best option to manage BTcP		6 (6-6)
B. Parenteral (iv/sc) opioids are the best option to manage BTcP		5 (4-4)
C. Short acting opioids are the best option to manage BTcP		5 (5-5)
3. Importance of BTcP characteristics in titrating dose of opioids according to peak intensity (1 not at all important -7 extremely important)		
A. Number of episodes/day		7 (6-6)
B. Dose and duration of action of each dose of opioids		6 (6-6)
C. Degree of relief after BTcP medication		6 (6-6)
D. Needs of additional BTcP medication for unrelieved pain (insufficient efficacy)		6 (5-5)
E. Previous need of increasing the total daily dose of medication		6 (5-5)
F. Side effect		6 (5-5)
4. The first follow-up visit after initiating the treatment of BTcP ?		**N (%),**
A. First 48 h after initiating the treatment		4 (8%)
B. 48-72 h after initiating the treatment		5 (10%)
C. As requested by the patient		4 (8%)
D. 3-7 days after initiating the treatment		18 (36%)
E. 7-15 days after initiating the treatment		11 (22%)
F. Next patient visit		8 (16%)

Note: BTcP=breakthough cancer pain.

Opioid Preference in Clinical Practice

Oxycodone (50%) was most frequently prescribed long acting opioids for background pain followed by fentanyl patch (39%), hydromorphone (7%), and slow releasing morphine (2%) (Figure 1A). Short acting oxycodone was the first drug of choice during the titration of opioids and 34% of respondent replied that they use transmucosal fentanyl when titrating long acting opioids (Figure 1B). Preference for BTcP medication were slightly different between inpatient and outpatient clinic (Figure 2). Short acting oxycodone was most frequently selected medication in both situation (inpatient setting vs. outpatient setting, p = 0.171) followed by transmucosal fentanyl formula (inpatient setting vs. outpatient setting, p = 0.271) (Figure 2).

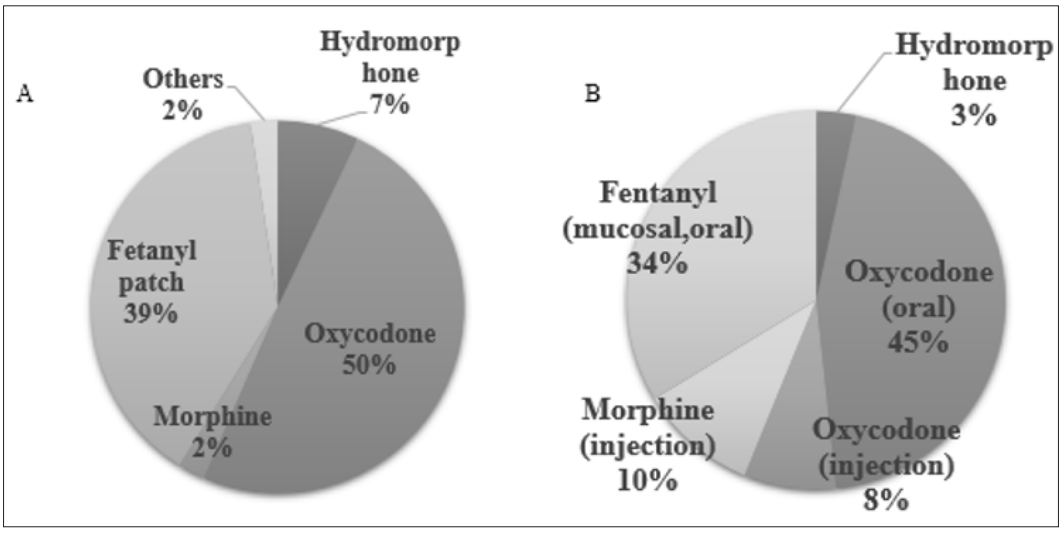

Figure 1: Long-acting opioids preferred in the management of background cancer pain (A). Short-acting opioids preferred in the opioid dose titration (B).

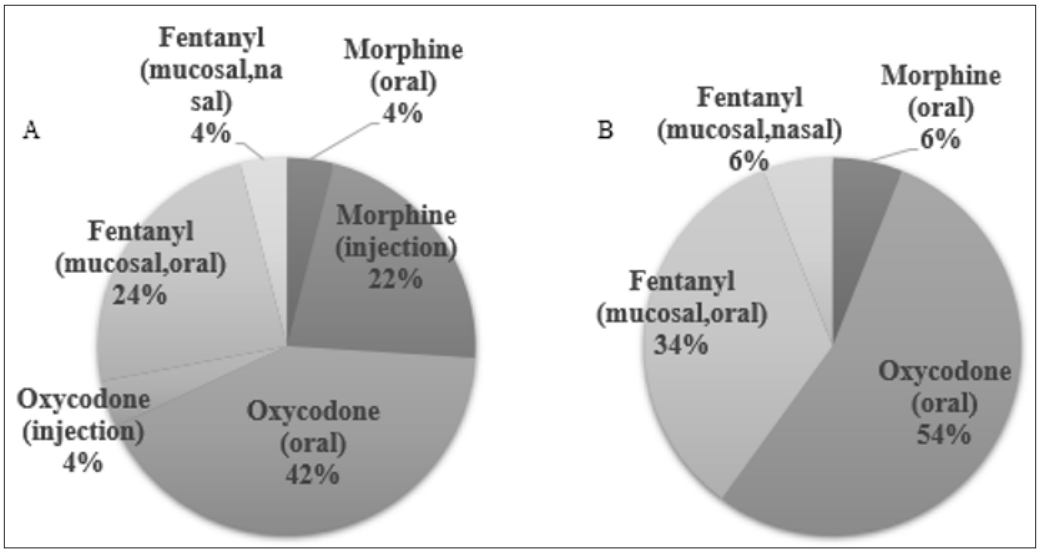

Figure 2: Rapid-acting opioids preferred in the management of breakthrough cancer pain in inpatient (A) and outpatient (B).

Results for Clinical Situation with Vignette

In the first case scenario, 38/50 of respondents chose to control background pain with opioid titration (answer D or answer A+E) and 6 of them answered they would like to add transmucosal fentanyl. Five were answered to use only transmucosal fentanyl for the case. Three were answered to increase the dose of long acting morphine and titrate with transmucosal fentanyl. Total 14 respondents replied that they will use transmucosal fentanyl in this case. Using transmucosal fentanyl in the case of uncontrolled background pain was not related to respondent's age (p = 0.13), years of experience (p = 0.86), and number of patients with opioids (p = 0.66). For the part of BTcP, 49 diagnosed as idiopathic breakthrough pain or unpredictable incidental pain and only one answered as predictable idiopathic pain. 37 answered to use transmucosal fentanyl and 11 chose short acting opioids instead of transmucosal fentanyl. One chooses to increase the dose of long acting opioids and the other chose to increase the dose frequency of long acting opioids. Using transmucosal fentanyl was not related to respondent's age (p= ?), years of experience (p = 0.67), and number of patients with opioids (p = 0.42).

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