An analysis of the variability of breakthrough pain intensity in patients with cancer

Allen W. Burton, MD,[a] Marilène Filbet, MD,[b] Alastair D. Knight, PhD,[c] Ravi Tayi, MD, MPH,[d] and Michael Perelman, MA, MB, BChir, FRCP[d]

[a]Houston Pain Associates, Houston, Texas; [b]Centre de Soins Palliatifs, Centre Hospitalier Lyon-Sud, Lyon, France; [c]Evicom Ltd, Teddington, England; and [d]Archimedes Development Ltd, Nottingham, England

Background The management of breakthrough pain in patients with cancer (BTPc) generally includes an initial titration of breakthrough pain medication to an effective dose, followed by the use of that dose in all subsequent episodes. This strategy presumes that an individual patient has a degree of consistency of pain during repeat episodes; however, that presumption has not been formally assessed.

Objective To examine the variation in pain intensity of BTPc episodes within individual patients and across patients.

Methods Data were pooled from two randomized, double-blind, crossover studies that used fentanyl pectin nasal spray (FPNS) vs comparator to relieve BTPc. Eligible patients were adults with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and adequately controlled background pain. The FPNS dose was titrated prior to a double-blind treatment consisting of 10 episodes. Pain intensity was reported on an 11-point numeric scale in which 0 = no pain and 10 = worst possible pain. Inter- and intrapatient variabilities of baseline pain intensity scores per episode were analyzed by analysis of covariance via a mixed-effect model. The influences of demographics and ECOG grade at study entry were assessed.

Results Mean baseline pain intensity score was 7.3 (standard deviation [SD], 1.76; range, 2-10) across 1,399 BTPc episodes in 152 patients. The interpatient variability of baseline pain intensity scores was 75.96%; intrapatient variability was 20.64%. Fixed terms for demographics and ECOG grade did not significantly influence baseline pain intensity score (≤ 5% level).

Limitations This was a post hoc analysis.

Conclusions Baseline pain intensity scores during episodes of BTPc vary widely between patients, but vary little within individual patients; this supports the use of a consistent maintenance dosage of analgesia for BTPc, once it has been titrated to an effective dose.

Funding/Support The study was funded by Archimedes Development Ltd.

Many patients with cancer experience pain; the rate is approximately 50% of patients across all populations,[1] but more than 70% of patients when the disease worsens.[2] In many cases, such pain can be managed by the use of long-acting agents (often opioids), but a significant proportion of patients experience acute exacerbations of their pain despite relatively stable and adequately controlled background pain.[3] Some studies report that more than 90% of patients with cancer pain suffer from breakthrough pain in cancer (BTPc).[4] Such breakthrough pain may be either spontaneous or related to a specific predictable or unpredictable trigger.[3] Patients with BTPc often experience psychological distress, including anxiety and depression, as well as reduced functionality, sleep impairment, and reduced enjoyment of life.[5-7] Therefore, managing BTPc treatment is important for maintaining or improving quality of life for many patients with cancer.[5-7]

It is generally accepted that BTPc is not a single entity, but has etiologies and clinical characteristics that vary from patient to patient during the course of the disease.[3,5,7-9] Some reports suggest that BTPc may vary in severity within the same patient over time.[3,5] To our knowledge, there are no published

Accepted for publication August 16, 2013. Correspondence: Marilène Filbet, MD; marilene.filbet@chu-lyon.fr. Disclosures: Dr Burton has served as a speaker for Archimedes Development Ltd, Cephalon Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, and Pfizer Inc; as a consultant for Medtronic Inc and Boston Scientific Corp; and is an equity shareholder/cofounder of Vapogenix Inc. Dr Filbet has received honoraria from Archimedes Development, Cephalon, Meda AB, and Nicomedes (now Takeda), and has received research funding from Archimedes Development, Cephalon, and Nicomedes. Dr Knight serves as a statistical consultant to Archimedes Development. Dr Tayi and Dr Perelman are employees at Archimedes Development. JCSO 2014;12:99-103. DOI 10.12788/jcso.0026.

data showing how pain intensity (severity) varies in individual patients across BTPc episodes.

Understanding whether there is variability in pain intensity may be important in the design of treatment strategies. The management of BTPc typically requires individual titration of the opioid analgesic to an effective dose.[3,10] However, if the severity of pain varies significantly within an individual patient from one episode of BTPc to the next, then one might intuitively expect more challenges in identifying a consistently effective dose for BTPc than if the severity of BTPc remains constant across episodes. Therefore, the main objective of this analysis was to examine the variation of pain intensity scores at the baseline (pretreatment) of BTPc between episodes in individual patients, as well as the variation across patients.

Methods

This post hoc analysis was based on pooled data from two randomized, double-blind, crossover studies, used to assess the efficacy of fentanyl pectin nasal spray (FPNS) in relieving BTPc (Studies 043 [NCT00459277][11,12] and 044 [NCT00589823][13,14]); the focus of this analysis is the pain intensity score reported by each patient during individual episodes of BTPc before rescue medication was administered. Although it was not specifically assessed, this was likely to be the worst pain experienced by the patient during that episode of BTPc. The two studies were conducted from 2006 through 2009 in 71 centers in the United States, Europe, Argentina, Costa Rica, and India. Full details of the study methodology can be found in the primary publications, but are briefly described below.[11–14]

Patient population

In both studies, eligible patients were adults with a histologically confirmed diagnosis of cancer, and an Eastern Cooperative Oncology Group (ECOG) grade ≤ 2.[11-15] They were to have had background (persistent) cancer-related pain that was controlled to moderate intensity or less by a fixed-schedule opioid regimen at a total daily dosage of ≥ 60 mg of oral morphine or an equivalent opioid for ≥ 1 week, and to have experienced, on average, 1 to 4 episodes of BTPc per day.[11-14] If a patient had more than one type or location of BTPc, only one was identified as the target BTPc for the assessment of efficacy.[11,13]

The most commonly reported cancer types were breast, bowel, lung, prostate, and pancreas. The most commonly reported background opioids were morphine (43%), fentanyl (23%), and oxycodone (15%). The mean morphine equivalent daily dose was 219.9 mg, with a large variation across the population (standard deviation [SD], 148 mg; range, 60 to 2,100 mg).

Study design

In this post hoc analysis, pain intensity scores that were recorded at the baseline of BTPc episodes during the double-blind treatment phase of two similarly designed studies were pooled (Figure 1).[11-14] Both studies had similar eligibility criteria and included an open-label, dose-titration phase in which FPNS was titrated to an effective dose (between 100 and 800 µg per episode of target BTPc) and a double-blind treatment phase, in which up to 10 episodes of BTPc were treated in each patient. In one study, 7 episodes were treated with FPNS and 3 episodes were treated with placebo;[11,12] in the other study, 5 episodes were treated with FPNS and 5 episodes were treated with immediate-release morphine sulfate.[13,14] At least 4 hours were to have elapsed between one dose of FPNS and the next (patients were permitted to take their usual BTPc analgesia as rescue medication if pain relief was inadequate, or if a separate episode of BTPc occurred before the next dose of FPNS was permitted). Because this analysis was confined to pain intensity scores that were recorded prior to the administration of the study drug, data from all BTPc episodes were included in the analysis regardless of treatment.

Assessments

Pain intensity at the baseline of each episode of BTPc was rated by the patient on an 11-point numeric scale (0 = no pain; 10 = worst possible pain) via an electronic diary.[11-14]

Statistical analyses

Analyses were conducted on pooled data from the modified intent-to-treat (mITT) population of both studies (n = 152; Figure 1). The mITT population consisted of all patients who completed the double-blind treatment phase and had both of the following: treatment for at least 1 evaluable BTPc episode with FPNS or the comparator, and a record of pain intensity at the baseline plus at least 1 post-baseline pain intensity measurement for each BTPc episode.[11,13]

The interpatient and intrapatient variabilities of pain intensity scores at the baseline of BTPc episodes were estimated from analysis of covariance (ANCOVA) using a mixed-effect model in which the following factors were included as fixed effects: age, ECOG grade, sex, race, and study; patient was included as a random effect. Coefficients of variation about the mean data were determined to provide alternative comparisons of interpatient and intrapatient baseline pain intensity score variability.

Results

Patient demographics

Data from 152 patients were included in the analysis. Most (70.4%) patients were aged ≤ 60 years; almost half (46.7%) of the patients were women; and most (87.5%) patients were white or Asian (Table 1).

Characteristics of baseline BTPc intensity

In all, 1,399 episodes of BTPc were treated among the 152

patients.[11,13] The mean pain intensity score at the baseline of each episode of BTPc was 7.3 (SD, 1.76) on a scale of 0 to 10, and the median pain intensity was 8 (range, 2-10); this intensity of pain is typical of the pain intensity reported in most other trials in the BTPc arena.[11,16-18]

Median pain intensity scores at the baseline of BTPc episodes were similar between patients aged ≤ 60 years (8) and those aged > 60 years (8), between men (8) and women (8), and across ECOG grades (7 to 8; Figure 2). Fixed terms for demographics and ECOG grade were not significant factors influencing baseline pain intensity scores at or below the 5% level (age, P = .0668; sex, P = .7583; ECOG status, P = .1032).

Interpatient and intrapatient variability in BTPc intensity

Interstudy variability accounted for only 3.40% of the total variability observed (Figure 3), which confirmed the homogeneity of scores between the two studies and validated pooling of the data. Pain intensity scores at the baseline of BTPc episodes varied more widely between patients than within patients: the interpatient variability was 3.68 times

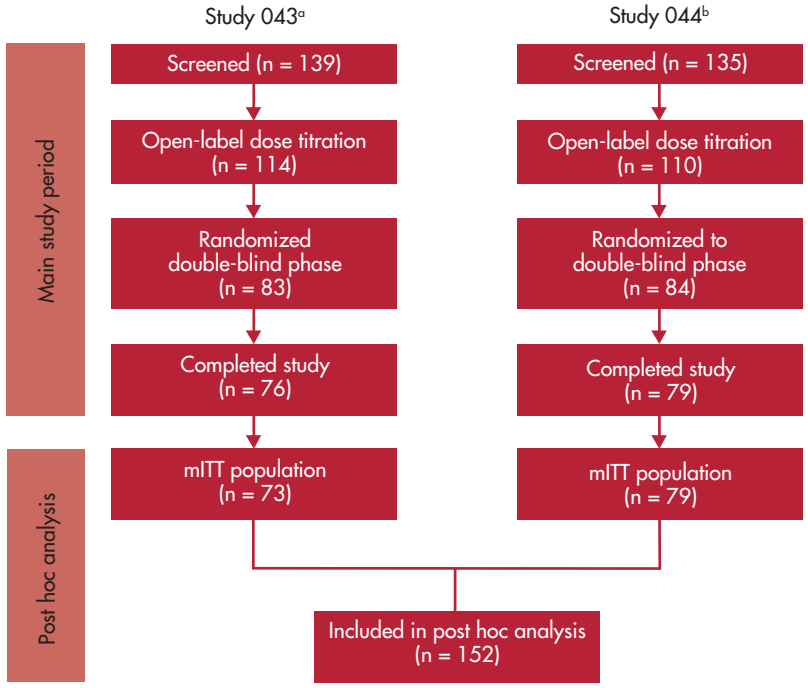

FIGURE 1 Study design and patient disposition

mITT, modified intent-to-treat
[a]Study 043 is NCT00459277.[11,12] [b]Study 044 is NCT005898230.[13,14]

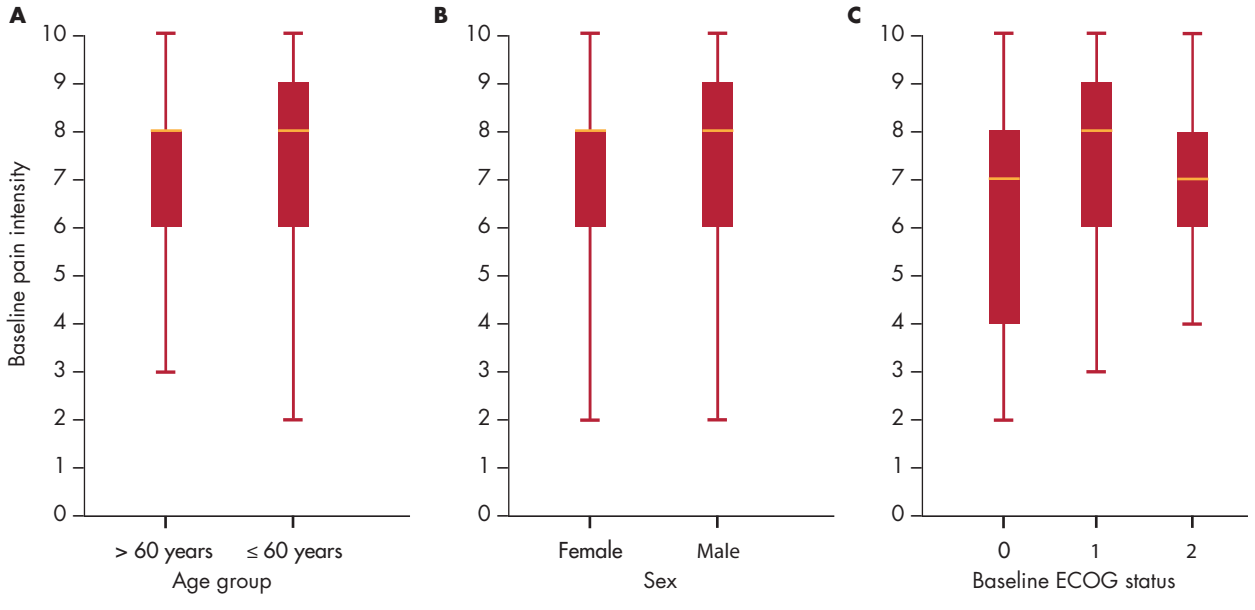

FIGURE 2 Baseline pain intensity scores in the modified intent-to-treat population (n = 152) did not differ significantly with age (P = .0668), sex (P = .7583), or Eastern Cooperative Oncology Group performance status (P = .1032). The box-and-whisker plots show the minimum value, 25% percentile, median, 75% percentile, and maximum value of baseline pain intensity scores. The median and 75% percentile values for patients older than 60 years and for women were both 8.

TABLE 1 Patient characteristics and ECOG performance status at baseline (N = 152, mITT population)

Characteristic	Study 043[a] (n = 73)	Study 044[b] (n = 79)	Total (N = 152)
Age, mean (SD), y	51.8 (11.9)	56.5 (11.7)	54.2 (12.0)
Female, n (%)	35 (47.9)	36 (45.6)	71 (46.7)
Race, n (%)			
White	53 (72.6)	33 (41.8)	86 (56.6)
Black	7 (9.6)	1 (1.3)	8 (5.3)
Southeast Asian	2 (2.7)	0 (0)	2 (1.3)
Asian Indian	0 (0)	45 (57.0)	45 (29.6)
Other	11 (15.1)	0 (0)	11 (7.2)
ECOG status,[c] n (%)			
0	10 (13.7)	4 (5.1)	14 (9.2)
1	42 (57.5)	48 (60.8)	90 (59.2)
2	21 (28.8)	27 (34.2)	48 (31.6)

ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat

[a]Study 043 = NCT00459277. [b]Study 044 = NCT00589823. [c]0 = fully active; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 = ambulatory and capable of all self-care, but unable to carry out any work activities.

greater than was the intrapatient variability, with the inter-patient variability accounting for 75.96% of the total variation in baseline pain intensity scores, compared with 20.64% for intrapatient variability.

Consistent with the 3.68-fold greater interpatient versus intrapatient variability that was demonstrated with the ANCOVA model, the interpatient variability (represented as a coefficient of variation based on the mean baseline BTPc episode score of 7.3) was 30.1%, compared with 8.2% for intrapatient variability.

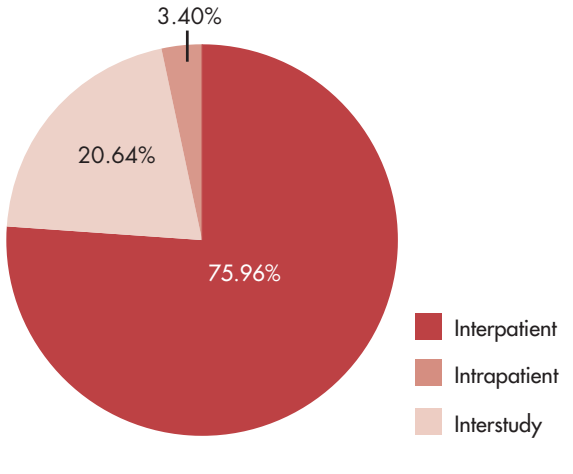

FIGURE 3 Interpatient and intrapatient variability in pain intensity scores in the modified intent-to-treat population (n = 152) at the baseline of breakthrough pain in patients with cancer episodes

Discussion

BTPc can substantially impair a patient's quality of life[19] and can result in increased health care costs from additional hospital visits, admissions, and longer in-hospital stays.[20] Therefore, ensuring adequate management of BTPc through a combination of around-the-clock therapy and as-needed, short-acting agents can offer meaningful benefits to the individual patient as well as to the economies of the health care system. Guidelines support the use of transmucosal fentanyl formulations for BTPc, because these preparations have a rapid onset of action and short duration of effect commensurate with the temporal characteristics of the pain.[21,22]

Numerous analyses have explored whether the maintenance dose of these transmucosal fentanyl preparations for BTPc can be predicted from factors such as the daily dosage of around-the-clock opioid medication,[3,21,23–25] the intensity of pain during the episode of BTPc,[9] or the dosage of a previously prescribed supplemental opioid (eg, fentanyl);[16,26,27] however, no clinically relevant relationships have been demonstrated. As such, the standard management strategy is to titrate each fentanyl preparation from its lowest dose to a maintenance dose, based on the patient's perspective of adequacy of analgesia, balanced against tolerability.[22] One assumption with this strategy is that the nature of the BTPc (eg, its duration and intensity) will be consistent within individual patients. This analysis has demonstrated that this assumption is broadly correct. Although the reported level of pain intensity at the baseline of the BTPc episodes varied widely among patients, the variation within individual patients was almost 4 times less, whether assessed via the ANCOVA model or the coefficient of variation. This consistency supports the strategy of managing BTPc with a consistent dosage of analgesic, once the individual's optimum dose is identified.

Further support for the findings of this analysis comes from a long-term study of FPNS (NCT00458510), which showed that the dosage of FPNS that was used to control BTPc did not need to be changed in the majority of patients who were treated over an extended period of time (up to more than 3 years)[28-30] These results suggest that the dose selected during titration is likely to continue to be successful during the long-term maintenance of the management of episodes of BTPc.

The limitations of this analysis include its post hoc and retrospective nature, although the collection of data used in the original trials was prospective and blinded with a relatively short duration during which the episodes of BTPc were captured (6.5 ± 3 days). Potential areas of future study could include assessing the variation of pain intensity over a longer period in a more prospective manner.

In conclusion, the results of this analysis demonstrated a wide variation in the pain intensity of BTPc episodes between patients; however, within individual patients, there

was little variation in pain scores between BTPc episodes. This finding endorses a BTPc management strategy for FPNS that incorporates an initial titration period followed by the use of the selected dose for long-term maintenance. This is also likely to be true for other agents.

Acknowledgments

Medical writing support and editorial assistance were provided by Karen Munro, Sharon Suntag, and Julie Gerke of Quintiles Medical Communications, Parsippany, New Jersey, and funding was provided by Archimedes Development Ltd, Nottingham, England.

References

1. Breivik H, Cherny N, Collett B, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol. 2009;20:1420-1433.
2. Portenoy RK, Lesage P. Management of cancer pain. Lancet. 1999;353:1695-1700.
3. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G; Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain. 2009;13:331-338.
4. Svendsen KB, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. Eur J Pain. 2005;9:195-206.
5. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain. 1999;81:129-134.
6. Payne R. Recognition and diagnosis of breakthrough pain. Pain Med. 2007;8(suppl 1):S3-S7.
7. American Pain Foundation. Breakthrough cancer pain: mending the break in the continuum of care. J Pain Palliat Care Pharmacother. 2011;25:252-264.
8. Portenoy RK. Treatment of temporal variations in chronic cancer pain. Semin Oncol. 1997;24(5 suppl 16):S16-S12.
9. Hagen NA, Fisher K, Victorino C, Farrar JT. A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials. J Palliat Med. 2007;10:47-55.
10. Fine P, Portenoy R. Strategies for opioid rotation: Decision support in chronic pain management. 2010. Available at: http://www.medscape.org/viewarticle/717832. Accessed December 26, 2012.
11. Portenoy RK, Burton AW, Gabrail N, Taylor D; Fentanyl Pectin Nasal Spray 043 Study Group. A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. Pain. 2010;151:617-624.
12. Taylor D, Galan V, Weinstein SM, et al. Fentanyl pectin nasal spray in breakthrough cancer pain. J Support Oncol. 2010;8:184-190.
13. Fallon M, Reale C, Davies A, et al; Fentanyl Nasal Spray Study 044 Investigators Group. Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study. J Support Oncol. 2011;9:224-231.
14. Davies A, Sitte T, Elsner F, et al. Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulfate in breakthrough cancer pain. J Pain Symptom Manage. 2011;41:358-366.
15. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.
16. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol. 2007;5:327-334.
17. Rauck R, North J, Gever LN, Tagarro I, Finn AL. Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. Ann Oncol. 2010;21:1308-1314.
18. Rauck R, Reynolds L, Geach J, et al. Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2012;28:859-870.
19. Portenoy RK, Bruns D, Shoemaker B, Shoemaker SA. Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 2: impact on function, mood, and quality of life. J Opioid Manag. 2010;6:109-116.
20. Abernethy AP, Wheeler JL, Fortner BV. A health economic model of breakthrough pain. Am J Manag Care. 2008;14(5 suppl 1):S129-S140.
21. Caraceni A, Hanks G, Kaasa S, et al; European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;13:e58-e68.
22. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Version 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive. Accessed December 26, 2012.
23. Zeppetella G, Ribeiro MD. Opioids for the management of breakthrough (episodic) pain in cancer patients. Cochrane Database Syst Rev. 2006;(1):CD004311.
24. Christie JM, Simmonds M, Patt R, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. J Clin Oncol. 1998;16:3238-3245.
25. Portenoy RK, Payne R, Coluzzi P, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain. 1999;79:303-312.
26. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain. 2001;91:123-130.
27. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain. 2006;22(9):805-811.
28. Portenoy RK, Raffaeli W, Torres LM, et al; Fentanyl Nasal Spray Study 045 Investigators Group. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients. J Opioid Manag. 2010;6:319-328.
29. Radbruch L, Torres LM, Ellershaw JE, et al. Long-term tolerability, efficacy and acceptability of fentanyl pectin nasal spray for breakthrough cancer pain. Support Care Cancer. 2012;20:565-573.
30. Taylor D, Radbruch L, Revnic J, Torres LM, Ellershaw JE, Perelman M. A report on the long-term use of fentanyl pectin nasal spray in patients with recurrent breakthrough pain. J Pain Symptom Manage. October 12, 2013. doi: 10.1016/j.jpainsymman.2013.07.012. [Epub ahead of print]