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Breakthrough pain management using fentanyl buccal tablet (FBT) in combination with around-the-clock (ATC) opioids based on the efficacy and safety of FBT, and its relationship with ATC opioids: results from an open-label, multi-center study in Japanese cancer patients with detailed evaluation

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Abstract

Objective: Rapid analgesic onset opioids, particularly fentanyl buccal tablet, is preferable for managing breakthrough pain. The efficacy and safety of fentanyl buccal tablet and its association with around-the-clock opioids needs to be explored with an option of dose adjustments, more closely reflecting administration in clinical practice. The aim of the study was to assess the safety and efficacy of fentanyl buccal tablet in breakthrough pain management in combination with around-the-clock opioids with the dose adjustment option, and explore the dose adjustment's influence on breakthrough pain management using detailed evaluation.

Methods: The 12-week open-label, multi-center study was conducted throughout Japan. Cancer patients aged 20 years or older, experiencing persistent pain controlled with around-the-clock opioids and breakthrough pain with supplemental medications were enrolled. Fentanyl buccal tablet and around-the-clock opioid doses could be adjusted under protocol-specified conditions. Efficacy variables were assessed at each fentanyl buccal tablet administration. Safety was assessed mainly by adverse events.

Results: All efficacy variables showed sustained analgesic effect. Nearly half the patients stayed on the same dose; most fentanyl buccal tablet administrations did not require additional supplemental medications. Dose increase of fentanyl buccal tablet and around-the-clock opioids seemed to

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improve breakthrough pain intensity and frequency, respectively. Fentanyl buccal tablet and around-the-clock opioid doses were not strongly associated. Treatment-related adverse events were all common with opioid treatment and did not increase over time.

Conclusions: Fentanyl buccal tablet can stably and safely manage breakthrough pain in cancer patients with independent dose adjustment based on detailed evaluation of each patient's condition. Breakthrough pain management using fentanyl buccal tablet with around-the-clock opioids at optimal doses may be an important factor in palliative care for cancer patients with breakthrough pain.

Key words: fentanyl buccal tablet, breakthrough pain, cancer pain, rapid-onset opioids, pain management

Introduction

Breakthrough pain (BTP) is a transient exacerbation of pain that occurs despite well-controlled background pain. BTP affects a high prevalence of cancer patients (1), and deteriorates their quality of life (QOL) (2–4). BTP can be controlled with supplemental 'rescue' medications. Short-acting opioids (e.g. immediate-release oral morphine and oxycodone) were conventionally used as supplemental medication, but they cannot successfully relieve BTP, due to its mismatched time-course (analgesic onset of ~30–60 min post-administration) with transitory characteristics of BTP (peak at 10 min or later, and duration of 60 min or longer) (2,5–7).

In contrast, rapid-onset opioids (ROOs) are designed to provide faster pain relief than conventional short-acting opioids (8–10). Fentanyl buccal tablet (FBT) in particular can achieve faster analgesic onset using newly developed technology that enhances the rate and extent of absorption through the buccal mucosa (11). The faster effects of FBT (as early as 10–15 min) (12–14) are apparent, compared with the analgesic onset of conventional supplemental medications (2,5,7). Thus, FBT that allows fast analgesic onset corresponding to the typical time course of BTP may be preferable for BTP management (5,15). Recently, the efficacy and safety of FBT for BTP in Japanese cancer patients has been assessed under a patient-optimized successful FBT dose in combination with background daily around-the-clock (ATC) opioids (16).

Supplemental oral morphine doses for BTP were initially recommended as a 4-hourly dose of ATC opioid for persistent pain (17) based on experience in palliative care practice and for the simplicity. Recently, the consensus recommends that these doses be individually identified (18). However, the recommendation was drawn based on a lack of association between the effective doses of FBT and baseline ATC opioid in a setting where the FBT dose was unchanged (12,14,19). Evaluation of the efficacy and relationship under the option of dose adjustment, as in clinical practice, may make it possible to suggest a practical dose regimen of FBT in combination with baseline ATC opioid dose for BTP management.

This article reports the safety and efficacy of FBT in BTP management in combination with ATC opioids in cancer patients under the option of dose adjustment and explored the influence of opioid dose adjustment on BTP management by using a detailed evaluation, an evaluation of the efficacy at each FBT administration at the dose adjusted for the individual patient.

Patients and methods

Study design

This was an open-label, multi-center study conducted at 34 sites in Japan from September 2007 to March 2009. This study enrolled cancer patients who participated in a double-blind, placebo-controlled trial that investigated FBT efficacy (rollover patients) (data not published) and cancer patients who were naïve to FBT (new patients). The study was approved by each institutional ethical committee and conducted in accordance with Good Clinical Practice. Written informed consent was obtained from each patient.

Patients

The study included patients aged 20 years or older with cancer pain due to solid or hematologic tumors confirmed by histological and cytological examination, and a life expectancy of 3 months or longer. Patients had to receive ATC opioid regimens (30–1000 mg/day of oral morphine or equivalent doses of opioids) to control their persistent pain for at least 1 week prior to enrollment, and also had to experience 1–4 BTP episodes a day that had been controlled with supplemental medications. Pre-study supplemental medications included FBT for rollover patients. Other key inclusion criteria included ability to evaluate their pain in a self-recording diary, and performance status due to cancer of Grade 0–2 as determined by the Eastern Cooperative Oncology Group (ECOG) assessment.

Exclusion criteria included disease or symptoms that may affect safety analysis (e.g. serious lung or heart disease), oral conditions that may interfere with FBT application (e.g. stomatitis), clinical disorders that may compromise data collection (e.g. psychological ones), or the following protocol-prohibited concomitant medications/treatment during the maintenance phases: monoamine oxidase inhibitors, narcotic antagonist analgesics, narcotic antagonists and drugs administered for other clinical trials.

Dose regimens

Before the maintenance phase, a FBT successful dose which was predefined to be the dose that provided sufficient pain relief without producing unacceptable adverse events (AEs) was identified by titration. During the 12-week maintenance phase, the FBT successful dose was administered for BTP episodes that occurred. The successful dose ranged from 100 to 800 μg for patients who received an ATC opioid dose of 60–1000 mg/day of oral morphine equivalents, and from 50 to 800 μg for those who received from 30 to <60 mg/day of oral morphine equivalents.

Administration of additional supplemental medications and dose adjustment of FBT or ATC opioids were considered as specified in the protocol during the maintenance phase. Patients were allowed to take additional supplemental medications including FBT when no pain relief was perceived by 30 min after FBT administration. When additional supplemental medications including FBT were frequently administered for one BTP episode or five or more BTP episodes occurred per day, adjustment of FBT or ATC opioid, respectively, was considered by the investigators. Investigators recorded any changes

in the FBT dose and the reasons for the changes. Patients were allowed to receive eight FBT administrations per day to treat a maximum of six BTP episodes per day. The seventh BTP episode and onwards in a day, or the BTP episode that occurred within 4 h after an FBT administration were treated with pre-study supplemental medications (except for FBT). These BTP episodes treated with pre-study supplemental medications were included in the number of BTP episodes.

Efficacy

Efficacy analysis was conducted on the maintenance efficacy analysis set including patients who had received at least one FBT dose and evaluated its efficacy at least once during the maintenance phase. For the efficacy evaluation, pain intensity (PI), pain relief (PR) and global medication performance assessment (GMPA), an overall impression of FBT treatment, were reported by patients for each FBT administration to assess the sustained analgesic effect.

PI was rated on an 11-point numeric rating scale (from 0 = no pain to 10 = worst pain imaginable) at pre (PI_0), 30 (PI_{30}) and 60 (PI_{60}) min post-administration. PR was rated on a 5-point ordinal scale (from 0 = no relief to 4 = complete relief from pain) at 30 (PR_{30}) and 60 (PR_{60}) min post-administration. GMPA was rated on a 5-point ordinal scale (from 0 = poor to 4 = excellent) at the same assessment points as PR ($GMPA_{30}$ and $GMPA_{60}$). Other major efficacy measures were pain intensity difference (PID) representing the change in PI at 30 and 60 min post-administration (PID_{30} and PID_{60}) from PI_0; and the sum of PID_{30} and PID_{60} ($SPID_{60}$).

Safety

Safety analysis was conducted on the safety analysis set, comprising all patients who received at least one FBT dose during the maintenance phase. The safety of 12-week treatment with FBT was evaluated based on the collected data on all recorded AEs, including vital signs, respiratory rates, arterial oxygen saturation (SpO_2) and frequency and severity of each event based on the oral and clinical examination during the maintenance phase. All AEs were coded according to the MedDRA/J version 11.1 System Organ Class and Preferred Term. Upon recording AEs, the grade was rated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0), as well as the likelihood of association with FBT evaluated by investigators. AEs were considered treatment-related when they were considered possibly, probably or definitely related.

Statistical analysis

Demographic and symptomatic characteristics at baseline were summarized descriptively; baseline was defined as the time at registration to the titration phase of the previous study for rollover and this study for new patients. One-way analysis of variance (ANOVA) was used to assess the assessment point (0–12 weeks) difference in mean score of the efficacy measures. Incidence of treatment-related AEs were calculated with 95% confidence intervals (CIs).

Additional exploratory analysis investigated three issues. First, mean and 95% CI of BTP frequency before and after ATC opioid dose increase was computed using the mean number of daily BTP episodes for 3 days before and after the ATC opioid dose increase. Second, mean and 95% CI of BTP intensity before and after ATC opioid dose increase was computed using the mean FBT efficacy evaluations of three BTP episodes before and after a dose increase. The mean and 95% CI of FBT dose increase was also explored in the same manner. One-way analysis of variance (ANOVA) was used to assess the assessment point (0–12 weeks) difference in mean dose in FBT and ATC opioid. Third, the association between the FBT and ATC opioid doses was explored using Spearman's correlation coefficient at 4-week intervals.

Calculation yielded 60 as the necessary sample size to detect AEs with a relatively high incidence of ~5% during the maintenance phase with a probability of 95%.

Statistical tests were two-tailed and conducted with a significance level of 0.05. SAS software version 8.2 (SAS Institute, Inc., Cary, NC) was used for statistical calculations.

Results

Overall, 82 patients were enrolled (Fig. 1). Of 51 rollover patients, 50 entered the maintenance phase and one discontinued due to consent withdrawal. As new patients, 31 underwent dose titration, and successful doses were identified for 26. Of them, one withdrew from participation at the investigator's discretion, and 25 new patients proceeded to the 12-week maintenance phase. The safety analysis set included 75 patients in total. Excluding one new patient for coadministered drug criteria violation during dose titration, 74 patients were included in the maintenance efficacy analysis set. In total, 41 patients completed the 12-week maintenance phase. A major reason for discontinuation was AEs, all of which were common in opioid treatment. No one discontinued due to a lack of treatment efficacy.

Table 1 shows the baseline demographic characteristics of the safety analysis set. The mean age (SD) was 59.5 (10.0) years. The most commonly used ATC opioids in the safety analysis set was fentanyl, followed by oral oxycodone and oral morphine. Oral morphine and oral oxycodone were the most commonly used supplemental medications. During the maintenance phase, the mean (SD) number of BTP episodes treated with FBT per patient was 108.7 (87.8), and the mean (SD) successful FBT dose to treat one BTP episode was 325.74 (207.58) μg.

The results of the main efficacy assessment are shown in Fig. 2. All efficacy variables showed sustained analgesic effect over 12 weeks. No efficacy measures were significantly affected by assessment points (0–12 weeks).

Treatment-related AEs were reported by 37.3% of the patients during the maintenance phase, and all were common with opioid treatment. The most frequently reported treatment-related AEs were somnolence (16.0%) and nausea (10.7%). Of 75 safety analysis set patients, discontinuation of the treatment due to AEs were reported in 12 patients; none of the AEs were treatment-related. Respiratory rates and SpO_2 also did not change notably over the maintenance phase.

Serious treatment-related AEs occurred in one patient, with one event each of nausea and vomiting. Five patients died during the entire study period, although none of the deaths were associated with FBT, but were rather due to the primary disease or complications.

No increase in the incidence of treatment-related AEs was observed during the maintenance phase (Table 2). Few AEs occurred for the first time after 2 weeks of this phase.

The successful dose (50, 100, 200, 400, 600 or 800 μg) distribution shifted to a higher dose at the end of treatment [1 (1.4%), 14 (18.9%), 20 (27.0%), 18 (24.3%), 15 (20.3%), and 6 (8.1%) patients] compared with the beginning [5 (6.8%), 21 (28.4%), 27 (36.5%), 7 (9.5%), 12 (16.2%) and 2 (2.7%) patients]. The reason for the dose change was insufficient efficacy ($n = 38$) followed by AEs ($n = 5$) and a change in the ATC opioid dose ($n = 4$ patients). FBT was administered a total of 7814 times; additional supplemental medications were used for 490 (6.3%) BTP episodes and of these, FBT was used for 187 (2.4%) BTP episodes.

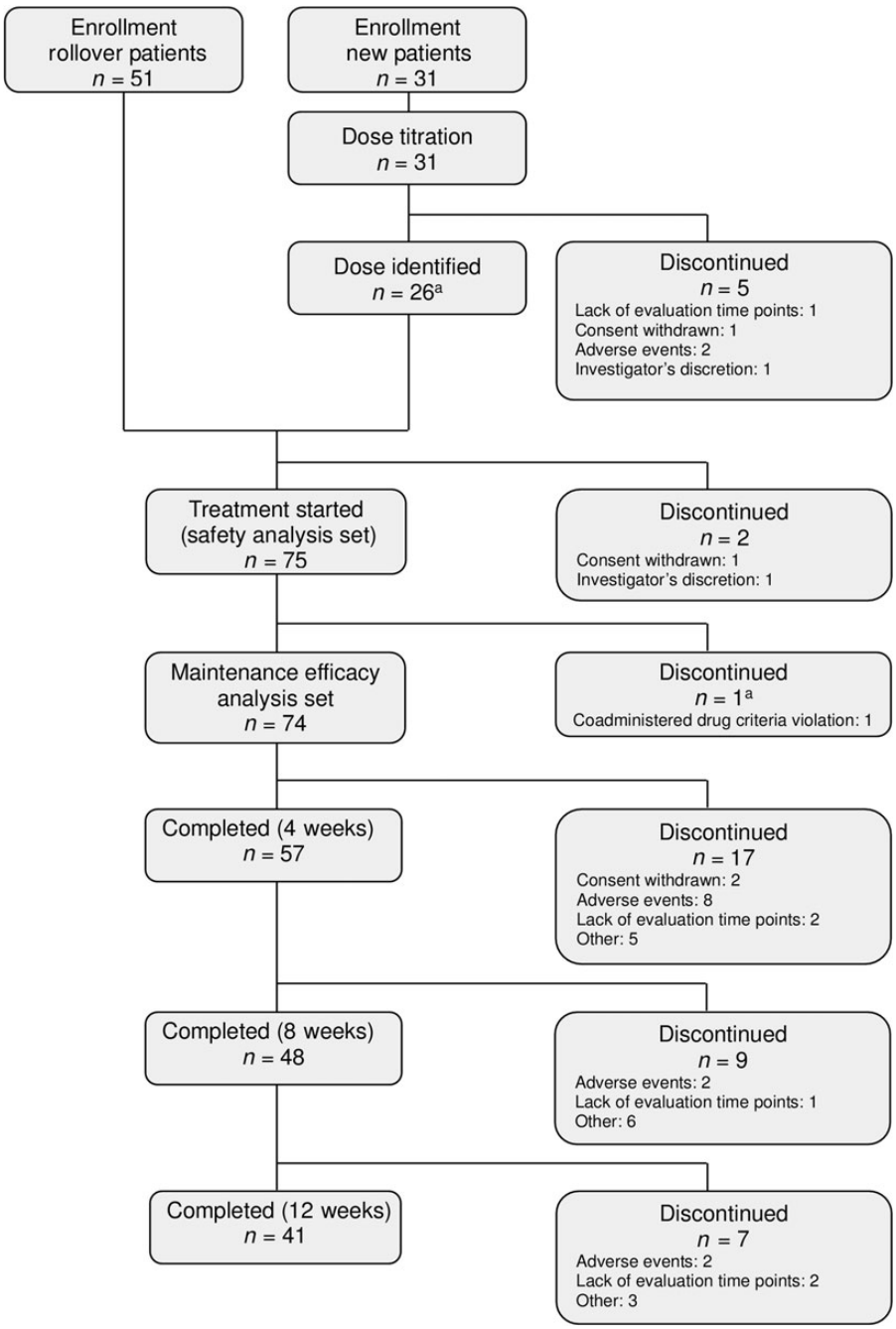

Figure 1. Patient flow. [a]The successful dose identified for one patient was later discontinued due to a coadministered drug criteria violation, and this patient was therefore not included in the efficacy analysis set.

Both the mean FBT and ATC opioid doses gradually increased over time from the beginning of the maintenance phase (Table 3). Significant influence of assessment points was detected in ATC opioid dose ($P < 0.05$). Although there was a similar chronologically increasing tendency, 32 (43.2%) patients continued taking the same successful FBT dose until they finished or discontinued their treatment. The FBT dose was changed in 42 patients (56.8%) (increased for 50 and decreased for 9 episodes). The ATC opioid dose was changed in 50 patients (67.6%) (increased for 94 and decreased for 13 times).

The ATC opioid dose was increased on 94 occasions; the mean number of daily BTP episodes decreased [mean change: 0.48 episodes (95% CI: 0.28–0.68), mean daily number ± SD before dose increase: 3.51 ± 1.35], and the PI_0 of BTP did not change (Table 4). After increasing the FBT dose, the mean PR_{30} and $GMPA_{30}$ slightly increased compared with those before the FBT dose increase (Table 5).

Strong associations between the FBT and ATC opioid doses were not found during the 12-week maintenance phase; Spearman's correlation ranged from $r = 0.446$ to $r = 0.674$ ($P < 0.0001$ for both).

Discussion

These results demonstrate that FBT has a sustained analgesic effect and was well tolerated for 12 weeks in combination with ATC opioids. Two key findings were indicated by the detailed evaluation, an

Table 1. Patient demographics at baseline

Demographics	Safety analysis set ($n = 75$)
Gender, *n* (%)	
Men	45 (60.0)
Women	30 (40.0)
Age, years, mean (SD)	59.5 (10.0)
Age of ≥65 years, *n* (%)	26 (34.7)
Weight, kg, mean (SD)	54.27 (11.11)
BMI, mean (SD)	21.01 (3.65)
Distribution of supplemental opioid usage, *n*[a,b]	
p.o. oxycodone	39
p.o. morphine	35
i.v./s.c. morphine	4
i.v./s.c. fentanyl	2
i.r. morphine	2
None	1[c]
Supplemental medication, mg/episode of oral morphine equivalents, mean (SD),	18.850 (18.604)
min, max	3.75, 110.00
Distribution of ATC opioid usage, *n*	
p.o. oxycodone	34
p.c. fentanyl	37
p.o. morphine	5
i.v./s.c. morphine	1
ATC medication, mg/day of oral morphine equivalents, mean (SD),	164.70 (160.74)
min, max	30.0, 840.0
BTP pathophysiology, *n* (%)[d]	
Nociceptive	43 (57.3)
Neuropathic	8 (10.7)
Mixed	24 (32.0)

BMI, body mass index; ATC, around-the-clock; BTP, breakthrough pain; FBT, fentanyl buccal tablet.

[a]FBT is not included in this supplemental opioid usage because the baseline of the rollover patients was the time at registration to titration phase of the previous study.

[b]Recorded for 1 week prior to dose titration.

[c]A patient had taken supplemental medications 2 weeks before registration. Thus the patient had been expected to have assessable BTP during the study period before registration. However, this patient did not take any supplemental medications for 1 week prior to the titration phase.

[d]BTP pathophysiology was summarized by the physicians' comprehensive diagnosis based on the patient report, image analysis, and pain related to cancer lesions.

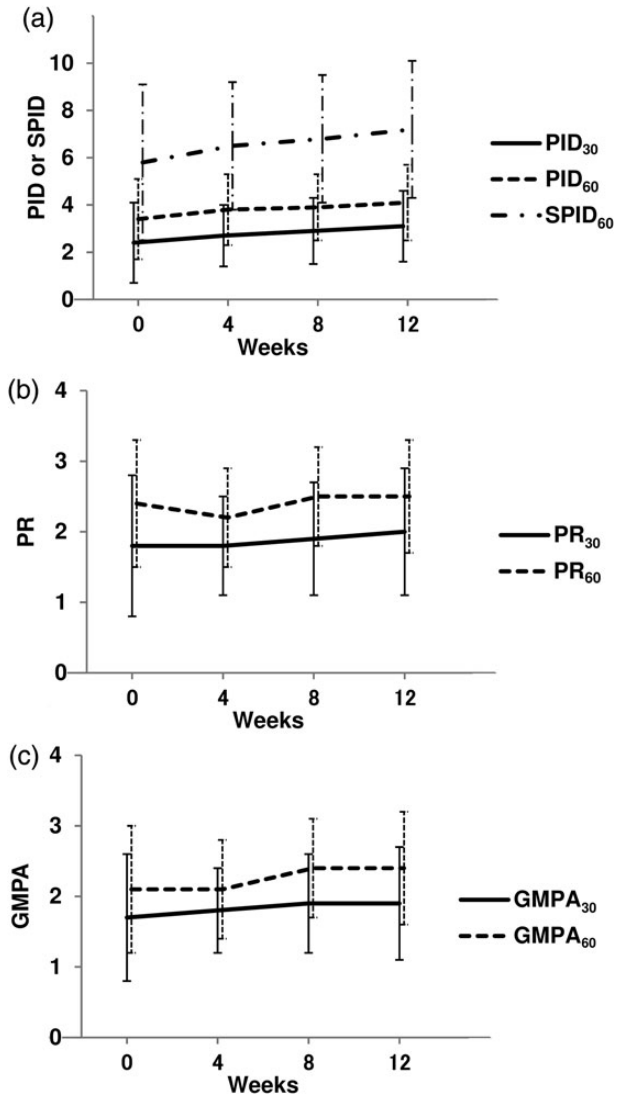

Figure 2. Efficacy evaluation items at 4-week intervals during the 12-week maintenance phase[a]. (a) PID_{30}, PID_{60} and $SPID_{60}$ at each assessment point. Assessment point difference in mean scores of PID_{30}, PID_{60} and $SPID_{60}$: $P = 0.1199$, 0.0726 and 0.0712, respectively, one-way analysis of variance (ANOVA). (b) PR_{30} and PR_{60} at each assessment point. Assessment point difference in mean scores of PR_{30} and PR_{60}: $P = 0.5625$ and 0.3493, respectively, one-way ANOVA. (c) $GMPA_{30}$ and $GMPA_{60}$ at each assessment point. Assessment point difference in mean scores of $GMPA_{30}$ and $GMPA_{60}$: $P = 0.4752$ and 0.1226, respectively, one-way ANOVA. PID: pain intensity difference; SPID: summed pain intensity difference; PR: pain relief; GMPA: global medication performance assessment. [a]Data are presented as mean ± SD.

evaluation of efficacy at each FBT administration with an option of dose adjustment of FBT and ATC opioids. First, ATC opioid dose increase seems to have a positive influence on BTP frequency, while FBT dose increase seems to have a positive influence on BTP intensity. Second, there was no strong association between FBT and ATC doses at 4-week intervals.

Throughout the maintenance phase, the analgesic effects achieved with FBT were well sustained and patients continued to have a good impression of FBT efficacy for 12 weeks. Once identified through titration, it was not necessary to change the dose in 43% of the patients. Furthermore, only a few of the FBT administrations required additional supplemental medications. The results suggest that BTP management would be successful by using FBT at a dose that is individually identified and adjusted based on the detailed evaluation of each patient's condition, in combination with background ATC opioids.

A similar trend of sustained satisfaction with FBT was reported in Western cancer patients over a longer period (20). QOL was reported to improve with stable or improved pain intensity (21,22). The interpretation of our present results and these reports may suggest a BTP management strategy to control BTP to alleviate psychological or social distress and eventually improve QOL. Management should be affected by the patients' cancer condition in clinical practice. However, considering the chronologically debilitating features of BTP, and the generally expected development of analgesic tolerance, our and previous results may suggest that BTP in cancer patients is manageable using FBT with ATC opioids, and the treatment may possibly lead to improvement in QOL.

Table 2. Summary of treatment-related adverse events reported in the safety analysis set

	2 weeks ($n = 75$)		4 weeks ($n = 71$)		8 weeks ($n = 62$)		12 weeks ($n = 50$)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Supraventricular extrasystoles	0 (0.0)	0.0, 4.8	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	1 (2.0)	0.1, 10.6
Ventricular extrasystoles	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Constipation	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	1 (1.6)	0.0, 8.7	2 (4.0)	0.5, 13.7
Dry mouth	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Nausea	5 (6.7)	2.2, 14.9	1 (1.4)	0.0, 7.6	1 (1.6)	0.0, 8.7	1 (2.0)	0.1, 10.6
Stomatitis	2 (2.7)	0.3, 9.3	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Vomiting	3 (4.0)	0.8, 11.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	1 (2.0)	0.1, 10.6
Drug tolerance	0 (0.0)	0.0, 4.8	1 (1.4)	0.0, 7.6	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Aspartate aminotransferase increased	0 (0.0)	0.0, 4.8	1 (1.4)	0.0, 7.6	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Blood bilirubin increased	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Blood glucose increased	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Gamma-glutamyl transferase increased	1 (1.3)	0.0, 7.2	1 (1.4)	0.0, 7.6	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Glucose urine present	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Protein urine present	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Urobilin urine present	0 (0.0)	0.0, 4.8	0 (0.0)	0.0, 5.1	1 (1.6)	0.0, 8.7	0 (0.0)	0.0, 7.1
Blood alkaline phosphatase increased	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Dizziness	2 (2.7)	0.3, 9.3	1 (1.4)	0.0, 7.6	1 (1.6)	0.0, 8.7	0 (0.0)	0.0, 7.1
Somnolence	7 (9.3)	3.8, 18.3	2 (2.8)	0.3, 9.8	2 (3.2)	0.4, 11.2	1 (2.0)	0.1, 10.6
Delirium	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Hallucination	0 (0.0)	0.0, 4.8	1 (1.4)	0.0, 7.6	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1
Hot flush	1 (1.3)	0.0, 7.2	0 (0.0)	0.0, 5.1	0 (0.0)	0.0, 5.8	0 (0.0)	0.0, 7.1

Table 3. The mean FBT and ATC opioid doses ($n = 74$)

	0 week	4 week	8 week	12 week	P value[a]
FBT dose (μg/episode), mean (SD)	272.3 (211.2)	298.2 (211.5)	305.2 (211.9)	308.5 (216.8)	0.774
ATC opioid dose[b] (mg/day), mean (SD)	162.1 (148.3)	212.2 (227.7)	235.9 (273.1)	291.2 (335.4)	0.047

[a]One-way analysis of variance.
[b]mg/day of oral morphine equivalent.

Table 4. Efficacy evaluation items before and after ATC opioid dose increase ($n = 91$ episodes[a])

	PI_0^b	PID_{30}^b	PR_{30}^b	$GMPA_{30}^b$
Before				
Mean (SD)	6.52 (1.76)	2.85 (1.43)	1.68 (0.82)	1.64 (0.83)
After				
Mean (SD)	6.49 (1.79)	2.91 (1.34)	1.76 (0.80)	1.69 (0.80)
Difference				
Mean (SD)	0.03 (0.62)	−0.05 (0.80)	−0.08 (0.57)	−0.05 (0.57)
95% CI	−0.10, 0.16	−0.22, 0.11	−0.20, 0.04	−0.17, 0.07

PI, pain intensity; PID, pain intensity difference; PR, pain relief; GMPA, global medication performance assessment.
[a]The number of ATC opioid dose increase episodes included in these data.
[b]Efficacy evaluations of FBT administrations for three BTP episodes before the ATC opioid dose increase and three episodes from the second episode treated with increased dose.

There was no upward tendency in the incidence of treatment-related AEs, all of which were common in opioids. This shows that up to 12-week FBT administration was well tolerated in Japanese cancer patients, which is consistent with 12-month (20) and 18-month studies (23). These results can be interpreted that FBT can be used safely for a long time, despite the expected dose increase over time due to the progressive nature of the disease (1,24).

Analysis of the association between FBT and ATC opioid doses did not yield a strong correlation, which is consistent with previous studies (12,14,19). The lack of a strong association between these two pain treatment regimens shown by the present analysis may be attributed to the mutually distinctive pain patterns including the intensity of BTP and persistent pain, and treatment using FBT and ATC opioids according to their patterns.

Based on the results of descriptive analyses before and after the FBT and ATC opioid dose increase, an ATC opioid dose increase decreased the number of daily BTP episodes and did not influence PI_0 of BTP. An FBT dose increase positively influenced the FBT efficacy evaluations. These results may suggest a basic and practical BTP management strategy: first, adjust the ATC opioid dose to reduce BTP

Table 5. Efficacy evaluation items before and after FBT dose increase ($n = 50$ episodes)

	PI_0^a	PID_{30}^a	PR_{30}^a	$GMPA_{30}^a$
Before				
Mean (SD)	6.50 (1.72)	2.74 (1.84)	1.53 (0.82)	1.55 (0.78)
After				
Mean (SD)	6.60 (1.80)	2.94 (1.68)	1.80 (0.71)	1.73 (0.70)
Difference				
Mean (SD)	−0.10 (0.63)	−0.20 (0.77)	−0.27 (0.61)	−0.17 (0.56)
95% CI	−0.28, 0.08	−0.42, 0.02	−0.45, −0.10	−0.33, −0.01

[a]Efficacy evaluations of FBT administrations for three BTP episodes before the FBT dose increase and three episodes from the second episode treated with increased dose.

frequency, which may lead to controlling persistent pain, and second, control BTP intensity by adjusting the FBT dose. In other words, clinicians may need to consider increasing the ATC opioid dose when the number of BTP episodes increases, and increasing the FBT dose when an FBT dose cannot achieve sufficient pain relief. The fundamental suggestion of this paper, namely, independent and individual dose identification and adjustment in BTP management using FBT in combination with ATC opioids, may be supported by the stable and safe BTP management and the lack of dose associations between FBT and ATC opioids found in this study. It should be noted that the data regarding this discussion is based on the occurrence of only less than a hundred FBT or ATC opioid dose increase episodes, a relatively small portion of the 7814 times in total that FBT was administered. However, this small number may be interpreted that the successful dose sufficed for most BTP episodes once identified through independent and individual titration.

There are some limitations in interpretation of our results. First, a single-arm, open-label design of this study does not allow inference of superiority of FBT over conventional supplemental medications or other pre-existing BTP management regimens. Second, QOL was not assessed; thus the influence of FBT on QOL needs to be explored further through direct evaluation. Third, the duration of this study is relatively limited, requiring future studies covering a longer evaluation period to derive a BTP management strategy more closely simulating clinical practice. Fourth, some of our interpretations were derived from additional analyses and may therefore need to be explored using a design suited for the objective of future studies.

In conclusion, FBT can stably and safely manage BTP in cancer patients for 12 weeks with independent dose adjustment based on detailed evaluation of each patient's condition. BTP management using FBT with ATC opioids at optimal doses may be an important factor in palliative care for cancer patients with BTP.

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Conflict of interest statement

Kenji Eguchi is a member of an advisory committee. All the other authors declare that there is no conflict of interest.

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