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Efficacy and safety of fentanyl inhalant for the treatment of breakthrough cancer pain: a multicenter, randomized, double-blind, placebo-controlled trial

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Abstract

Background Breakthrough cancer pain (BTcP) has a negative impact on patients' quality of life, general activities, and is related to worse clinical outcomes. Fentanyl inhalant is a hand-held combination drug-device delivery system providing rapid, multi-dose (25μg/dose) administration of fentanyl via inhalation of a thermally generated aerosol. This multicenter, randomized, placebo-controlled, multiple-crossover, double-blind study evaluated the efficacy, safety, and tolerability of fentanyl inhalant in treating BTcP in opioid-tolerant patients.

Methods The trial was conducted in opioid-tolerant cancer patients with 1 ~ 4 BTcP outbursts per day. Each patient was treated and observed for 6 episodes of BTcP (4 with fentanyl inhalant, 2 with placebo). During each episode of targeted BTcP, patients were allowed up to six inhalations, with an interval of at least 4 min between doses. Primary outcome was the time-weighted sum of PID (pain intensity difference) scores at 30 min (SPID30).

Results A total of 335 BTcP episodes in 59 patients were treated. The mean SPID30 was -97.4 ± 48.43 for fentanyl inhalant-treated episodes, and -64.6 ± 40.25 for placebo-treated episodes ($p < 0.001$). Significant differences in PID for episodes treated with fentanyl inhalant versus placebo was seen as early as 4 min and maintained for up to 60 min. The percentage of episodes reported PI (pain intensity) scores ≤ 3, a ≥ 33% or ≥ 50% reduction in PI scores at 30 min, PR30 (pain relief scores at 30 min) and SPID60 favored fentanyl inhalant over placebo. Only 4.4% of BTcP episodes required rescue medication in fentanyl inhalant group. Most AEs were of mild or moderate severity and typical of opioid drugs.

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Conclusion Treatment with fentanyl inhalant was shown to be a promising therapeutic option for BTcP, with significant pain relief starting very soon after dosing. Confirmation of effectiveness requires a larger phase III trial.

Trial registration ClinicalTrials.gov: NCT05531422 registered on 6 September 2022 after major amendment, NCT04713189 registered on 14 January 2021.

Keywords Breakthrough cancer pain, Inhaled fentanyl, Rapid-onset opioid, Cancer pain

Introduction

Approximately 60% of cancer patients experience transient episodes of breakthrough pain that occurs on a background of relatively well-controlled baseline pain [1, 2]. Typically, breakthrough cancer pain (BTcP) has a rapid onset and reaches its peak within several minutes: episodes may be spontaneous or precipitated by movement or other triggers [3]. Frequent bursts of BTcP (up to 4 times per day) have a negative impact on patients' quality of life (QoL), general activities, and is related to worse clinical outcomes [4–6].

Efforts have been made to seek "rescue treatments" for BTcP during the past decades. Oral opioids including hydrocodone, hydromorphone, morphine, and oxycodone are widely used as traditional treatments. However, the barrier of gastrointestinal tract and first-pass metabolism makes it difficult to match with the rapid onset and short duration of a BTcP episode. Thus, there remains a need for formulations with pharmacokinetic and pharmacodynamic features that better match the profile of BTcP episodes. Actiq® is the first oral transmucosal fentanyl formulation [7]. It's supposed to be absorbed through oral mucosa and presents pharmacokinetic profile characterized by a high early fentanyl concentration. After Actiq®, various transmucosal routes have been developed, including buccal, sublingual, and intranasal [8–12]. Intranasal fentanyl such as Instanyl® (fentanyl nasal spray) and PecFent®(fentanyl pectin nasal spray) present higher bioavailability and faster onset compared to Actiq®. These products are benefiting patients in many countries but not yet marketed in China.

Fentanyl inhalant is a unique formulation with a handheld combination drug-device delivery system providing rapid, consistent multi-dose administration of fentanyl via inhalation of a thermally generated aerosol. The device is consisted of disposable dose cartridges containing fentanyl which are inserted into a reusable controller. The dose cartridge portion of the product contains 25 stainless steel foils, each coated with a unit dose (25 μg) amount of fentanyl. The dose cartridge has a mouthpiece at one end and a plastic airflow control valve on the bottom of the cartridge. Patients are supposed to seal their lips firmly around the mouthpiece and inhale deeply and fully, taking in as much air as possible. Oral inspiration through the product triggers the heating though a breath sensor in the airway and generates an aerosol of excipient-free fentanyl with a particle size distribution for efficient delivery to the deep lung and into the systemic circulation. After initiation of inhalation, vaporization of the entire drug coating and aerosol formation is complete in less than 1 s. The pharmacokinetics of inhaled fentanyl are similar with administration by IV. Absolute bioavailability was 90.5% based on nominal coated dose [13].

The primary objective of this study was to demonstrate the efficacy of fentanyl inhalant in treating BTcP comparing with placebo. Secondary objective was to evaluate the safety and tolerability of the inhaled fentanyl.

Methods

Study design

This multicenter, randomized, placebo-controlled, double-blind, multiple-crossover study was conducted at 14 centers in China. Patients were supposed to stay at the hospital for no longer than 8 days.

The protocol was approved by Ethics Committee of Sun Yat-sen University Cancer Center Ethics Committee (A2021-038–01, A2021-038-X02 after major amendment). This clinical trial was executed in accordance with the ethical and scientific principles of the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice (ICH GCP), as well as the applicable requirements of National Medical Products Administration (NMPA) guidelines. Written informed consent was obtained from all patients prior to enrollment. The trail was prospectively registered at ClinicalTrials.gov (registered as NCT05531422 after major amendment, registration date: 6 September 2022; initially registered as NCT04713189, registration date: 14 January 2021).

Patients

Adult men or women who had a histologically confirmed diagnosis of cancer, receiving a fixed-schedule opioid regimen at a total daily dose equivalent to or greater than 60 mg oral morphine per day for background pain, and had one to four episodes of moderate to severe (defined as ≥ 4 scores on an 11-point numerical rating scale) BTcP per day were eligible. Background pain must had been well-controlled (scored as ≤ 4 on an 11-point numerical rating scale) for at least

1 week before enrollment. Other key inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, adequate hematologic, hepatic, renal functions and Pulmonary function, willingness and ability to comply with study procedures.

Major exclusion criteria included pregnancy; past inability to tolerate fentanyl or other opioids,; severe clinical conditions including brain metastases, myasthenia gravis, bronchial asthma; history of operation within 3 weeks; use of treatment (such as chemotherapy) within 1 week that might impact the patient's assessment of pain or response to pain medication; use of monoamine oxidase inhibitors within 2 weeks; participation of any other clinical studies within 1 month; inability to assess and score the intensity of pain independently.

Procedures

Consenting patients who met eligibility criteria were allowed to enter the study. Medication for background pain during screening were maintained until the end of the study. Each patient would be treated and observed in sites for 6 episodes of targeted BTcP. Patients were randomly assigned to 1 of the 6 prespecified dose sequences which were established by a computer-generated schedule of active drug and placebo in a 4:2 ratio. All patients and personnel involved with the study (including investigators and investigative site personnel) were blinded to the medication codes. The randomization codes for each study sites were kept in sealed envelopes (one per drug pack), to be opened only in medical emergencies.

Patients were admitted to centers at Day1, received study medication for all 6 episodes, finished the end-of-study visit within 48 h after last dose, then got permission to leave. Before the first dose of study medication, every patient would take training for breathing maneuver and be taught how to use the device properly. Patients were instructed to exhale fully, then inhale briskly and completely through the device, and hold that breath for 10 s. During each episode of targeted BTcP, patients were allowed up to 6 inhalations with an interval of at least 4 min. The treatment of one episode ended when pain intensity was NRS (numerical rating scale) ≤ 3. A maximum of 4 episodes of BTcP per day could be treated with study drugs with an interval of at least 2 h between episodes.

If the patients did not perceive adequate pain relief 30 min after dosing, they were allowed to take a dose of their usual rescue medication (i.e. subcutaneous injection of morphine). Patients also were instructed that an interval of at least 4 h was to elapse between the use of rescue medication and the next dose of study drug. Any occurrence of acute pain other than the target BTcP could be treated using rescue medication.

Efficacy outcome measures

Electronic data capture system was used to collect patient data during the study. Baseline pain intensity (PI) before treating an episode of BTcP was recorded using an 11-point NRS ("0" = no pain,"10" = worst pain conceivable). Pain intensity scores were then self-assessed and recorded at 4, 8, 12, 16, 20, 30 and 60 min after the first dosing of each targeted episodes. Pain relief (PR) was assessed before and 30 min after the first dosing using a 5-point categorical scale (1 = no relief; 2 = a little relief; 3 = moderate relief; 4 = a lot of relief; 5 = complete relief). Details of any rescue medication were required, including time of usage and dose.

Safety and tolerability assessments

Safety and tolerability were assessed by monitoring adverse events throughout the study, clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), measurement of vital signs (heart rate, blood pressure, respiratory rate, and temperature), oxygen saturation, physical examination and cardio-pulmonary function (pulmonary function tests, oxygen saturation and electrocardiogram). Blood samples for clinical laboratory evaluations and cardio-pulmonary function tests were taken during screening and within 48 h after the end of treatment. Vital signs and oxygen saturations were recorded at baseline, 15 min, 30 min, 1 h and 2 h after last dose of every targeted episode. Any change was noted, and the clinical significance of any abnormal findings was judged. Concomitant medications were monitored throughout the study.

Statistical analysis

In this phase 2 study, we planned to recruit a total of 60 patients.

All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina). Efficacy analysis was primarily performed on full analysis set (FAS) population, which was defined as all randomized patients who received study medication and had ≥ 1 subsequent pain assessment. Safety analyses were performed on safety population, which was defined as all patients who received ≥ 1 of study medication.

The primary endpoint was the SPID at 30 min (SPID30). SPID30 was calculated as the time-weighted sum of PID scores at 30 min, and derived as follows: SPID30 = (PID4 × 4 + PID8 × 4 + PID12 × 4 + PID16 × 4 + PID20 × 4 + PID30 × 10). SPID is widely reported in clinical

trials of pain, which summarizes treatment response over a clinically relevant period. The specific calculation formula varies based on the design of different trials.

Secondary efficacy endpoints included: PID (pain intensity difference between each time points and predose) at 4, 8, 12, 16, 20, 30, and 60 min after first inhalation of each episode; SPID at 60 min; the proportion of BTcP episodes with an pain intensity ≤ 3, and with an improvement in pain intensity scores > 33% and > 50% after dosing; PR score at 30 min; and the proportion of BTcP episodes requiring rescue medication.

Linear interpolation method and last-observation-carried-forward (LOCF) method were used to input missing PI scores and PI scores after rescue medication intake. The primary efficacy parameter, SPID30, was analyzed using a mixed model of repeated measures with treatment (fentanyl or placebo), BTcP episode and baseline pain intensity score as fixed factors, and subject as random factor. Secondary endpoints including differences in PID between treatments at each time point, SPID60 and PR30 were analyzed using a model similar to the primary endpoint. In addition, the number and percentage of episodes in each treatment group achieving PI scores ≤ 3 and with an improvement in PI scores > 33% and > 50% were summarized and compared between treatments. Descriptive statistics were used for the description of the study population, baseline characteristics, and safety parameters.

Report of this study was organized following CONSORT reporting guidelines [14].

Results

Patient disposition and baseline demographic characteristics

The study was conducted at 14 clinical sites in China between 20 October 2021 and 27 April 2023. A total of 84 patients were screened and 60 were enrolled in the study (Fig. 1). Fifty-nine patients took study medication and were included in the final full analysis set and safety population. One patient withdrew from the study before first dose and got excluded from both datasets. A total of 6 (10.0%) patients of full analysis set discontinued the study. The reasons for discontinuation were withdrawal consent (3 patients, 5.0%), adverse events (1 patients, 1.7%), lack of efficacy (1 patients, 1.7%), inability to take the drug due to advancing cancer (1 patients, 1.7%).

The demographic and baseline characteristics of the study population are summarized in Table 1. The mean age of the patients was 58.3 years old. And 62.7% of them were male. The median duration of cancer was 2.01 years. The most commonly used background pain medication were oxycodone hydrochloride (39.0%) and fentanyl (11.9%). Half (50.8%) of the safety population had been treated for BTcP.

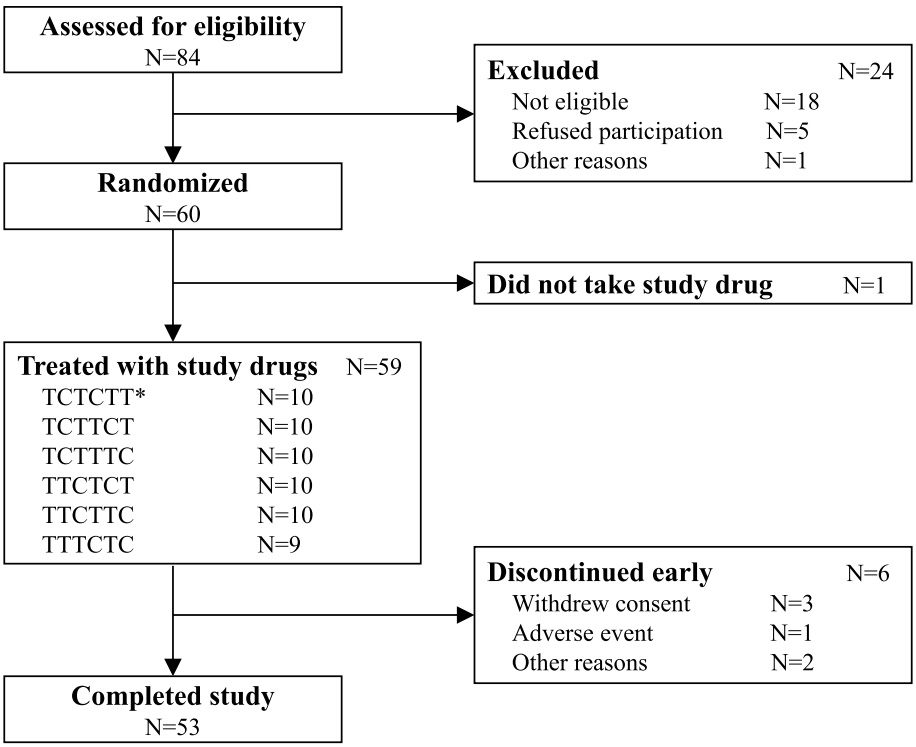

Fig. 1 Flow diagram through trial

Table 1 Baseline demographic characteristics

	Safety population (*N* = 59)
Age, mean (SD), y	58.3 (10.27)
Sex, no. (%)	
Female	22 (37.3)
Male	37 (62.7)
Weight, mean (SD), kg	57.99 (10.952)
Height, mean (SD), cm	163.45 (8.041)
Primary tumor type, no. (%)	
Digestive cancer	25 (42.4)
Lung cancer	12 (20.3)
Urogenital cancer	6 (10.2)
Other	16 (27.1)
Time since diagnosis of cancer, mean (SD), y	2.01 (2.503)
Mean (SD) no. of episodes of BTcP per day	2.063 (0.8189)
ECOG performance status, no. (%)	
0	5 (8.5)
1	29 (49.2)
2	24 (40.7)
Previous cancer treatment, no. (%)	
Chemotherapy	42 (71.2)
Surgery	3(5.1)
Radiation	2(3.4)
Background pain medications, no. (%)	
Oxycodone hydrochloride	23 (39.0)
Morphine sulfate/Morphine/Morphine hydrochloride	13(22.0)
Fentanyl	7 (11.9)
Other	16(27.1)

ECOG Eastern Cooperative Oncology Group, *SD* standard deviation

Table 2 Mean (SD) PID (pain intensity difference) at different time points

Time Point	Fentanyl Inhalant (*N*=225)	Placebo (*N*=110)	Deference[a]	P
4 min	-1.1 (0.09)	-0.6 (0.11)	-0.4 (0.10)	<0.001
8 min	-2.0 (0.15)	-1.2 (0.16)	-0.8 (0.12)	<0.001
12 min	-2.7 (0.17)	-1.9 (0.19)	-0.9 (0.13)	<0.001
16 min	-3.4 (0.18)	-2.3 (0.20)	-1.0 (0.13)	<0.001
20 min	-3.8 (0.18)	-2.7 (0.20)	-1.1 (0.14)	<0.001
30 min	-4.2 (0.18)	-3.1 (0.19)	-1.1 (0.13)	<0.001
60 min	-4.4 (0.17)	-3.4 (0.18)	-1.0 (0.13)	<0.001

[a] Difference is calculated as (fentanyl inhalant PID) - (placebo PID)

Efficacy

The efficacy analyses were performed on 335 BTcP episodes for 59 patients. A total of 225 episodes of BTcP treated with fentanyl inhalant and 110 episodes with placebo were included. At baseline, the mean PI score was 6.1 for fentanyl inhalant-treated episodes, and 6.0 for placebo-treated episodes.

A significant difference was revealed in primary efficacy endpoint—SPID30. The mean ± SD was -97.4 ± 48.43 for fentanyl inhalant-treated episodes, and -64.6 ± 40.25 for placebo-treated episodes. After adjustment for the treatment in the mixed covariance model, a statistically significant treatment effect in favor of fentanyl inhalant was also reported ($p < 0.001$), with a mean treatment difference of -27.7 (least squares means, -94.2 (4.49) for fentanyl inhalant and -66.5 (4.86) for placebo). The difference of SPID enlarged at 60 min with a mean treatment difference of -57.9 (least squares means, -231.4 (105.14) for fentanyl inhalant and -162.2 (91.21) for placebo, $p < 0.001$). Significant differences in PID for episodes treated with fentanyl inhalant versus placebo were seen as early as 4 min after dosing, and significant differences were maintained for up to 60 min, the last time interval assessed (Table 2, Fig. 2).

At 30 min, 92.9% of BTcP episodes treated with fentanyl inhalant and 75.5% with placebo reported PI scores ≤ 3 ($p < 0.001$). For 225 episodes treated with fentanyl inhalant, over half of them only needed 3 inhalations (75 μg) or less. Eleven percent of episodes needed 1 inhalation (25 μg) before PI scores NRS ≤ 3, 24.9% needed 2 inhalations (50 μg), 17.3% needed 3 inhalations (75 μg) (Fig. 3). At 30 min, 92.0% of BTcP episodes treated with fentanyl inhalant and 79.1% of those managed with placebo reported a ≥ 33% reduction in PI scores ($p = 0.008$). A ≥ 50% reduction in PI scores was observed for 84.4% of BTcP episodes in the fentanyl inhalant group and for 66.4% in the placebo group ($p = 0.002$). PR scores were significantly greater for inhaled fentanyl compared with placebo at 30 min (3.8 verses 3.1; $p < 0.001$). Rescue medication was used in 4.4% of BTcP episodes treated with inhaled fentanyl and 12.7% of those receiving placebo ($p = 0.02$).

Safety and tolerability

During the study, 111 treatment-emergent adverse events (TEAEs) were reported by 40 patients (67.8%). The most common TEAEs (those occurring in > 10% of patients) were constipation (16.9%), nausea (13.6%), emesis (11.9%), hypoalbuminemia (11.9%) and anemia (10.2%). The majority of TEAEs were mild to moderate in intensity. Sixteen patients (27.1%) had one or more investigator-assessed treatment-related adverse events (TRAEs), most of the TRAEs were grade 1 or 2, only 1 patient (1.7%) developed a grade 3 hypertension, and no grade 4 TRAE were observed (Table 3). The common TRAEs were constipation, hypertension, and dizziness. Eight patients died during the study. None of these deaths

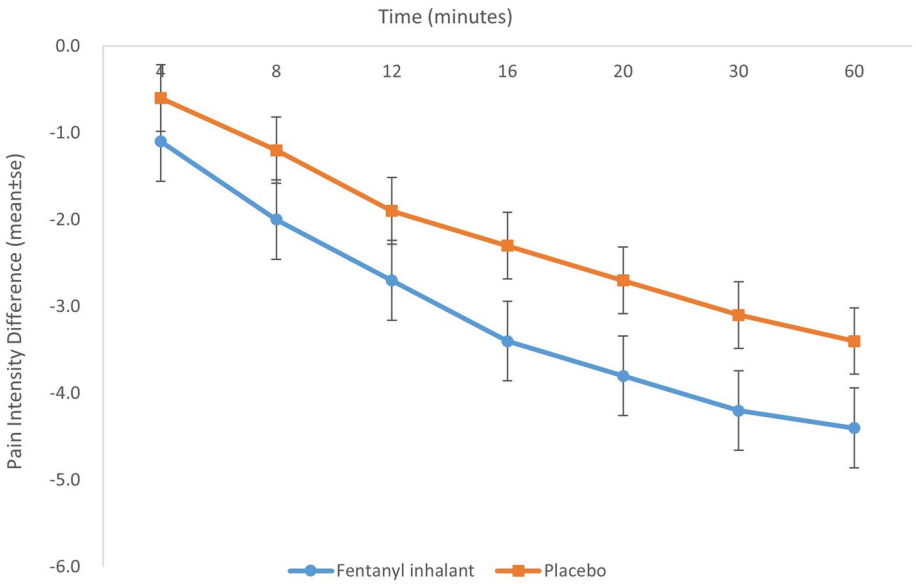

Fig. 2 Mean PID (pain intensity difference) over time

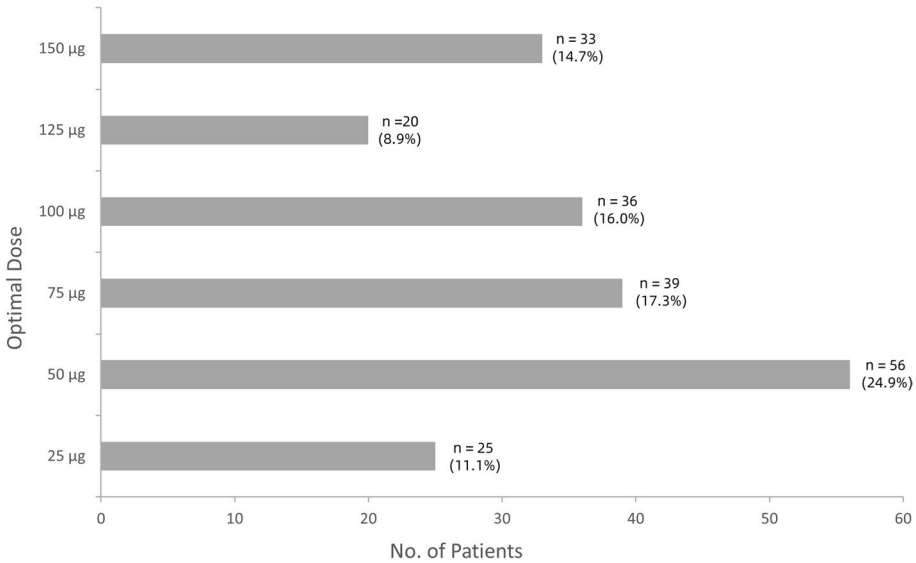

Fig. 3 Optimal dose among the FAS population

were considered related to the study drug, but rather due to progression of the underlying cancer. Other serious adverse event (grade 1 fever resulting in prolonged hospitalization) occurred in only one patient (1.7%) which were considered by the investigator to be probably related to study drug. One patient (1.7%) withdrew from the study because of TEAE (hypertension and dizziness). All TEAEs or TRAEs were relieved or stable after symptomatic treatment. Respiration rate and oxygen saturations were stable after dosing. Minor decrease to under 95% but above 91% occurred in 15 (6.7%) episodes after inhaling fentanyl.

Discussion

It has been reported that more than half of patients receiving prescription medicine for cancer pain experience inadequate pain relief or breakthrough pain [15]. Several rapid onset transmucosal fentanyl formulations

Table 3 Common adverse events

Adverse Event	Incidence, n (%) [nAE]
TEAEs occurring in >10% of patients	
Constipation	10 (16.9) 10
Nausea	8 (13.6) 8
Emesis	7 (11.9) 9
Hypoalbuminemia	7 (11.9) 7
Anemia	6 (10.2) 6
TRAEs occurring in >1 patients	
Constipation	6 (10.2) 6
Hypertension	3 (5.1) 8
Dizziness	3 (5.1) 4
Nausea	2 (3.4) 2
Emesis	2 (3.4) 2
Fever	2 (3.4) 2

TEAE treatment-emergent adverse event, *TRAE* treatment-related adverse event

were used to deal with BTcP in the United States and other countries. In China, clinical choices for BTcP are more limited. Immediate-release morphine tablets was the most common and only recommended opioid for out-patients. However, the delay of onset of analgesia mismatches the natural characteristics of BTcP, in which the median interval from onset of pain to its peak has been reported to be just a few minutes [3].

This is the first study to examine the efficacy, safety, and tolerability of fentanyl inhalant in the treatment of BTcP. The study met its primary endpoint: fentanyl inhalant was efficacious for pain, as indicated by a statistically significant improvement in SPID30 compared with placebo ($p < 0.001$). Fentanyl inhalant produced significantly greater reductions in pain intensity compared with placebo beginning 4 min after drug administration and continuing through 60 min.

Overall, fentanyl inhalant was safe and well tolerated during the study. The most common TEAE was constipation and nausea which were normally seen in clinical trials of other fentanyl formulations, including lozenge, soluble film, and tablet formulations, and no new safety concerns were identified.

The design of this study is different with trials evaluating efficacy and safety of other fentanyl formulations for BTcP. An open-label dose titration phase to identify a tolerable but effective dose (an enrichment approach [16]) was not adopted in this study. Every treatment of BTcP was a titration. Patients were supposed to take one more inhalation (25 μg) if their self-assessment for pain intensity was NRS > 3, and to stop whenever they feel unable to tolerate. Only one patient discontinued because of lack of efficacy.

Fentanyl inhalant presented a rapid onset treating BTcP which was consistent with the pharmacokinetic characteristics determined in previous studies [4]. Compared with transmucosal formulations, inhaled fentanyl disperses with the rapid airflow of inhalation, delivered extensively to the distal airways with rapid absorption across the alveolar membrane into the pulmonary capillaries. The optimal dose of other marketed fentanyl formulations is over 200μg for most patients [17]. In this study, inhaled fentanyl at a dose up to 150μg relieved 92.9% of BTcP, over half of which only needed 75μg before NRS ≤ 3. It seems like that fentanyl inhalant provided a rapid analgesic effect with a much lower dose compared with fentanyl via buccal, sublingual, or nasal. All the studies performed with these delivery systems was preformed amongst opioid-tolerant patients receiving doses of oral morphine equivalents of at least 60 mg. A lower mean baseline pain intensity (6.0 for fentanyl inhalant vs. 6.3 ~ 7.0 for transmucosal fentanyl) might have contributed to a lower mean required dose. Moreover, the greater efficiency of pulmonary drug delivery system compared with transmucosal drug delivery system must be addressed when explain such a huge dose difference. An enormous alveolar surface area with epithelium, consisting of a thin single cellular layer, promotes efficient gas exchange through passive transport, but also provides a mechanism for efficient drug delivery into the bloodstream [18]. For indications like BTcP, rapid absorption is highly valued giving how fast an episode peaks.

Several factors may affect drug absorption via inhalation. The efficiency of absorption is dependent upon the dose deposited and its distribution within the lung. Respiratory diseases, such as cystic fibrosis and chronic bronchitis, change the architecture of the lung through alterations in bifurcation angles and obstruction of the airways due to mucus accumulation, modifying the deposition and distribution patterns of aerosols. In patients with low FEV1 (severe obstruction), aerosol distribution was extremely uneven with predominately central airway deposition compared with the uniform distribution characteristic of patients with unobstructed airways [19]. Smoking, on the other hand, does not seem to delay drug absorption. In studies of aerosol insulin and inhaled terbutaline, the pulmonary absorption was significantly higher in healthy smokers than non-smokers [20, 21].

Abuse, overdose, and addiction of fentanyl has caused an increasing public health threat in several countries [22, 23]. Prolonged or high-dose use of fentanyl can lead to physical dependence and addiction, contributing to substance use disorder [24]. Fentanyl inhalant provided adequate pain relief with much lower doses compared with marketed formulations, which might result in less addiction. The drug-device delivery system plus an

intelligent cloud monitoring system could be an option for drug control. Patients are instructed to unlock the device with a registered fingerprint before every inhalation, and the device is locked for 4 min before the next inhalation. Every related activity including prescription, purchasing, registration, unlocking, and consumption, will be uploaded and supervised.

This study has a number of limitations, and the data must be interpreted appropriately. A placebo effect is normally seen in clinical trials, and stronger in studies related to pain therapies: 87.3% of episodes treated with placebo did not require additional rescue medication. There are possible explanations for such a high placebo response. High expectation was built after the treatment of inhaled fentanyl because every patient was treated with both fentanyl and placebo with crossover design [25]. And it is possible that a proportion of episodes could have relieved spontaneously within a short time. Though, early results were hardly affected because the median duration of a BTcP episode was reported to be 45 ~ 60 min [26]. Furthermore, patients received both fentanyl inhalant and placebo; hence it may have been difficult to attribute adverse effects to either treatment.

Conclusion

In conclusion, fentanyl inhalant could be a promising option with great efficacy and acceptable safety profile in the management of BTcP. A rapid onset of effect was observed, with statistically significant reductions in pain intensity starting 4 min after first inhalation and continuing through 60 min. Based on these findings, a phase III, randomized clinical study is being approved.

Abbreviations

BTcP	Breakthrough cancer pain
PID	Pain intensity difference
SPID	Sum of pain intensity difference
PI	Pain intensity
PR	Pain relief
QoL	Quality of life
IV	Intravenous
ICH GCP	The International Conference on Harmonization Guideline for Good Clinical Practice
NMPA	National Medical Products Administration
ECOG	Eastern Cooperative Oncology Group
NRS	Numerical rating scale
FAS	Full analysis set
LOCF	Last-observation-carried-forward
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event

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Authors' contributions

Y.H., J.W., and D.L. were leading principal investigators of this study. They contributed in designing and reversing of the protocol, provided patients and leaded the conduction of study. R.L., B.S., N.L., B.R., J.B., Y.L., W.W., A.L., S.L., B.L., P.C. provided patients and conducted this study. Y.W. and Y.L. wrote the main manuscript text. X.Y. and X.L. (Xueying Liu) managed the process of study and data aquisition. X.D. and X.L. (Xiaoyi Li) provided the idea and supervision. All authors reviewed the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from Ethics Committee of Sun Yat-sen University Cancer Center (A2021-038–01, A2021-038-X02 after major amendment). All participants in this study provided written informed consent for the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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