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Original Article

Safety and Efficacy of Oxycodone in Cancer Patients with Moderate-to-Severe Cancer Pain: A Single-Medical Center Experiences

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Abstract

Background: The study aimed at evaluating the safety and tolerability of oxycodone in patients with moderate-to-severe cancer pain at a medical center in southern Taiwan. **Materials and Methods:** This was a subgroup analysis of a 12-week, uncontrolled, open-label, multicentric study. During the treatment phase, all participants received control-released (CR) oxycodone and/or immediate-released (IR) oxycodone. The primary end point was the number and percentage of patients with adverse events (AEs) and serious adverse events (SAEs). The secondary end points included patient-reported outcomes and titration of oxycodone. **Results:** A total of 19 patients were enrolled at this medical center. A total of 56 AEs were documented in 12/19 (63.2%) patients, of which, only 4/56 (7.1%) AEs were treatment-related adverse events occurring in 3/19 (15.8%) patients and no treatment-related SAEs were observed. Most AEs were mild and typical for opioids administered to patients with cancer pain. The most AEs involved the gastrointestinal systems (23%), such as nausea, constipation, and vomiting. At the study end, pain intensity of Numeric Rating Scale score had significantly decreased from 6.3 to 1.6 points; the quality of life on the European Quality of Life Visual Analog Scale (EQ-VAS) median score had improved from 50 to 60 points; and proportion of good/excellent quality of analgesia (QoA) had increased from 5.3% to 100%. The interesting findings of EQ5D item analyses that the top two improvements were anxiety/depression and pain/discomfort, whereas "mobility" and "self-care" became worse, demonstrated that improvement in cancer pain seems to have more improvement on patients' anxiety/depression." The median stable dose was 20 mg/day and the median time to reach stable dose was 1 day. **Conclusion:** CR and IR oxycodone are tolerable and effective in managing moderate-to-severe cancer pain among patients with colorectal cancers s at this medical center. Neither new safety signals nor significant bowel function disorders were noted. Together with the high acceptability and improvements on anxiety/depression and pain/discomfort on Taiwanese cancer patients, CR and IR oxycodone can be another valuable pain management option used for the daily control of moderate-to-severe cancer pain.

Keywords: Cancer pain, oxycodone, patient-reported outcomes, safety, tolerability

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Introduction

Moderate-to-severe pain is a common symptom of cancer, and it affects 70%–80% of patients with advanced disease. If poorly treated, it can adversely affect patients' physical functioning, psychological well-being, and social interactions.[1] Strong opioids are the mainstay of analgesic therapy in treating moderate-to-severe cancer pain, and morphine has been the accepted gold standard for the treatment of cancer pain endorsed by the European Association of Palliative Care and other important cancer pain guidelines.[2-5] Although opioids have proven the analgesic efficacy, the use is frequently complicated by a range of side effects including nausea, sedation, euphoria, dysphoria, constipation, and itching. The most common and debilitating side effect is opioid-induced bowel dysfunction, which comprises a constellation of gastrointestinal adverse events (AEs) such as constipation, hard dry stools, straining, incomplete evacuation, bloating, abdominal cramping, abdominal distension, and increased gastric reflux, among which, constipation is the primary symptom of opioid-induced bowel dysfunction occurring in approximately 90% of cancer patients receiving opioid therapy.[6-9]

Oxycodone is a strong opioid used firstly in Germany in 1917 and displays a significant affinity to both μ-opioid and κ-opioid receptors. OxyContin® (oxycodone hydrochloride control-released [CR]) tablets and OxyNorm® (oxycodone hydrochloride immediate-released [IR]) capsules were developed with the aim of reducing opioid-related gastrointestinal side effects. With the new technology of CR formulation, the analgesic effect can be initiated in 1 h and last for 12 h.[10] Plasma concentrations of oral oxycodone are far more predictable than that of morphine. Oxycodone possesses high oral availability with less interindividual variation, a rapid onset of action, an absence of a ceiling dose,[11,12] and lower incidence of adverse effects.

The effectiveness and tolerability of CR and IR oxycodone in patients with cancer pain have been previously studied.[13] Forty-eight patients were randomly divided into CR and IR groups, and received titrated dose up to 400 mg/day. There was no difference in the titration scheme between CR and IR oxycodone and the mean daily dose was 104 mg and 113 mg, respectively. The percentage of patients with pain controlled was 92% for the CR group and 79% for the IR group. The mean time to get pain controlled was 1.6 and 1.7 days, respectively, for the CR and IR groups. The occurrence rate of adverse reaction was also similar in both groups.

Despite oxycodone has been widely used in Western countries for more than 20 years, oxycodone has just been available in Taiwan since 2015. Majority of the physicians do not have much experience of using oxycodone in cancer pain management. Herein, this study aimed at evaluating the safety profile and efficacy of oxycodone in patients with moderate-to-severe cancer pain.

Materials and Methods

Study design

This was a 12-week, uncontrolled, open-label, multicentric study to evaluate the long-term safety and tolerability of CR and IR oxycodone in patients with moderate-to-severe cancer pain in Taiwan. After providing written informed consent, eligible patients were evaluated every 2 weeks after the baseline visit (the first prescription of oxycodone) until week 12. During the 12-week treatment phase, all patients received 10- or 20-mg CR oxycodone tablet and/or 5-mg IR oxycodone capsule. Opioid analgesic drugs other than oxycodone were not allowed to use. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. The Research Ethics Committee of study centers approved the study protocol (IRB No. 201601013A4, 20-Sep-2016), and all patients provided written informed consent.

Population

Eligible patients were aged 20 years or older, with cancer pain at moderate-to-severe intensity (Numeric Rating Scale [NRS] score ≥4), requiring treatments with continuous around-the-clock strong opioid analgesic, and having Eastern Cooperative Oncology Group score ≤2. Patients or their caregivers had to be able to fill out the questionnaires and willing to participate in the study by providing written informed consent. Patients were excluded from the study for the following reasons: evidence of noncancer pain or unexplained pain; constipation (Common Terminology Criteria for Adverse Events grade ≥3); significant structural/functional abnormalities of gastrointestinal tract or planned to undergo high-risk surgeries leading to gastrointestinal stenosis, blind loop, or gastrointestinal obstruction; abnormal lab results with obvious clinical significance, such as creatinine ≥2 folds of upper limit of normal (ULN) value, aspartate transaminase/alanine transaminase ≥2.5 folds of ULN (≥5 folds for patients with liver metastasis or primary liver cancer), or liver function of Child C grade prior to study; moderate-to-severe psychiatric problems; and hypersensitivity to oxycodone. Pregnant or lactating women, patients who had drug/alcohol abuse, those who were clinically unstable, or had a life expectancy of <3 months were also excluded from the study.

End points and assessments

The primary end point was the number and percentage of patients with AEs and serious adverse events (SAEs). The secondary end points included patient-reported outcomes such as pain intensity assessment using NRS; the quality of life (QoL) assessment using European QoL Questionnaire (EQ-5D) with Visual Analog Scale (EQ-VAS); and the quality of analgesia (QoA) measured as excellent, very good, good, fair, or poor; the average time to reach the stable dose (i.e., a daily dose fixed for at least 2 weeks) and the stable dose in the first titration; and reasons for treatment discontinuation.

Regarding safety assessments, any new AEs that occurred or worsened in intensity and/or frequency after providing written informed consent were recorded during the 12-week treatment phase until 2 weeks after the end of the study or early withdrawal from the study. The intensity of AEs and potential correlation between AEs and oxycodone were judged by the physicians. In addition, vital signs and physical examinations were conducted every 4 weeks for safety monitoring.

The pain intensity, assessed by a verbally administered 0–10-point NRS referred to the pain level evaluation at a fixed time daily as possible (e.g., every evening or before sleep), was recorded at every study visits. The QoL assessment, EQ-5D, was conducted every 4 weeks after the baseline visit. EQ-5D is a standardized instrument for measuring generic health status in terms of five dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[14] This study used the VAS (range 0–100) of EQ-5D to measure the overall QoL. Opiate withdrawal symptoms were assessed using COWS at baseline and the end of the study or early withdrawal from the study. This instrument includes the following 11 common opiate withdrawal signs or symptoms: resting pulse rate, sweating, restlessness, pupil size, bone or joint aches, runny nose or tearing, gastrointestinal upset, tremor, yawning, anxiety or irritability, and gooseflesh skin. The sum of symptom scores can be used to assess patients' physical dependence on opioids (mild: 5–12; moderate: 13–24; moderately severe: 25–36; and severe: >36).

Statistical analysis

The statistical analyses were mainly descriptive. The number of observation, mean, median, standard deviation (SD), minimum, maximum, and 95% confidence intervals were presented for the continuous variables. Changes in continuous variables over time were evaluated by paired *t*-test or Wilcoxon signed-rank test when the data strongly indicated a violation of normal assumption. Categorical data were tabulated as frequency and percentage. $P < 0.05$ was considered statistically significant. The last observation carried forward (LOCF) procedure was used to estimate the missing data except for safety.

Results

Patient demographic and baseline characteristics

Demographic and baseline characteristics are shown in Table 1. The mean age of all the enrolled patients was 63.1 years, with 52.6% of patients aged ≥65 years. Male patients accounted for 63.2% of the enrolled patients.

Among the enrolled 19 patients, 15 patients were with rectum cancers, 3 patients were with colon cancers, and 1 patient was with cervix uteri cancer [Table 1]. Among the 19 cancer patients, 6 patients were diagnosed at the early stage and the rest of the patients were at the advanced stage (multiple organ metastasis).

Table 1: Patient demographics

Variable/status	ITT population (*n*=19)
Age (years)	
Mean (SD)	63.1 (11.74)
Median (minimum-maximum)	65.0 (36-82)
95% CI	57.45-68.76
Age groups, *n* (%)	
20-40	1 (5.26)
41-64	8 (42.11)
≥65	10 (52.63)
Gender, *n* (%)	
Male	12 (63.16)
Female	7 (36.84)
Body height (cm)	
Mean (SD)	162.6 (6.82)
Median (minimum-maximum)	163.0 (146-173)
95% CI	159.35-165.92
Body weight (kg)	
Mean (SD)	57.63 (7.008)
Median (minimum-maximum)	56.30 (46-74.5)
95% CI	54.254-61.009
ECOG performance status, *n* (%)	
0	1 (5.26)
1	15 (78.95)
2	3 (15.79)
Disease duration (years)*	
Mean (SD)	4.815 (6.1162)
Median (minimum-maximum)	2.050 (0.07-24.1)
95% CI	1.8673-7.7632
Categorization of primary cancer (multiple options), *n* (%)	
Colon	3 (15.79)
Uterus or cervix	1 (5.26)
Rectum	14 (73.69)
Rectosigmoid colon	1 (5.26)
Metastasis, *n* (%)	
Yes	13 (68.42)
No	6 (31.58)
Distribution of metastasis (multiple options)**, *n* (%)	
Lung	9 (69.23)
Liver	6 (46.15)
Lymph node	10 (76.92)
Bone	3 (23.08)
Peritoneal	1 (7.69)
Pelvic	3 (23.08)

*Disease duration=(ICF date − primary cancer diagnosed date + 1)/365.25, **The number of patient(s) in the category/the number of patient(s) who had metastasis (*n*=13). SD: Standard deviation, ECOG: Eastern Cooperative Oncology Group, CI: Confidence interval, ICF: Informed consent form, ITT: Intention to treat

Primary end point – safety

Overall, CR and IR oxycodone were well tolerated in the 12-week observation. A total of 56 AEs were documented in 12/19 (63.2%) patients, of which, only 4/56 (7.1%) AEs were treatment-related adverse events (TRAE) occurring in 3/19 (15.8%) patients and no treatment-related SAEs were observed. Most AEs were mild and typical for opioids administered to patients with cancer pain [Table 2]. The most

AEs involved the gastrointestinal systems (23%), such as nausea, constipation, and vomiting. The four TRAEs were mild in severity (Grade II), and all belonged to gastrointestinal system (nausea, vomiting, and constipation). Regarding eight SAEs, none of them were judged as TRAE. The eight SAEs were caused by infectious or other diseases, such as sepsis, pneumonia, urinary tract infection, cardiac arrest, and hematochezia. Two patients died of sepsis and cardiac arrest during the study period.

Secondary end points

Pain intensity in terms of NRS score had significantly decreased from 6.3 to 1.6 points at week 12 [$P < 0.0001$, Figure 1]. Concerning the patient satisfaction on pain management, the proportion of good/excellent quality of anesthesia (QoA) had increased fast from 5.3% to 100% at week 8 and sustained 100% at week 12 [Figure 2].

On an average, it took about 4.2 days to titrate to the stable dose. The median time to reach the stable dose was 1 day, implying that the enrolled patients could get to the stable dose quickly and have adequate pain control within 5 days. The mean (SD) stable dose was 20.8 (6.4) mg/day and the median stable dose was 20.0 mg/day, indicating that oxycodone administered at 20 mg/day was able to control the moderate-to-severe cancer pain in this patient population [Table 3].

The QoL of the cancer patients receiving oxycodone treatment was also evaluated using the EQ-5D-3 L questionnaire. The median EQ-5D VAS score at baseline was 50 and the score at the end of treatment (EOT) was 60, whereas the mean EQ-5D VAS score at baseline was 51.5 and 49.75 at EOT.

When conducting a detailed analysis of the numbers and dimensions of EQ5D at baseline and EOT, improvements on EOT were observed at "pain/discomfort" and "anxiety/depression," when comparing the data of "difference of patient with problems" between baseline and EOT [Table 4]. The ranking of level change showed that "anxiety/depression" and "pain/discomfort" were the top two improvements indicating that the enrolled patients receiving oxycodone treatments for their cancer pain showed improvements on anxiety/depression and pain/discomfort, whereas "mobility" and "self-care" became negative improvements that may be caused by the disease progress status.

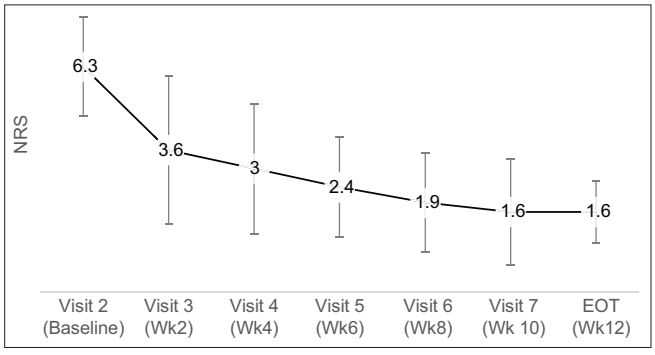

Figure 1: Average Numeric Rating Scale score during study periods

Discussion

Opioids are the standard of care to relieve moderate-to-severe pain in cancer patients, and morphine, oxycodone, and hydromorphone have been recognized by the WHO and other cancer pain guidelines as the 1st line treatment of moderate-to-severe cancer pain. As oxycodone becomes available in Taiwan from 2015,[3-5] there was no local clinical research concerning the usage of oxycodone for Taiwanese cancer patients. Results from this study demonstrate that CR and IR oxycodone were well tolerated while providing favorable analgesia in terms of pain control and QoL to patients with moderate/severe cancer pain. The majority of AEs were typical ones that have been documented on the local labeling. Although constipation was still found to be one of the most common AEs, only one constipation event was suspected to be related to oxycodone treatment.

Without the safety concerns regarding opioid-induced bowel dysfunction, CR and IR oxycodone in this study were well accepted by Taiwanese patients with cancer pain, with improved QoL and high acceptability of treatment that over 90% of patients rated the quality of analgesia as good or excellent. The treatment acceptability was even higher than those reported previously, where 73%–80% of the participants rated IR and CR oxycodone as of good and excellent acceptability in Stambaugh's study,[15] and the mean acceptability of therapy in Parris' study was fair to good throughout the study period.[16]

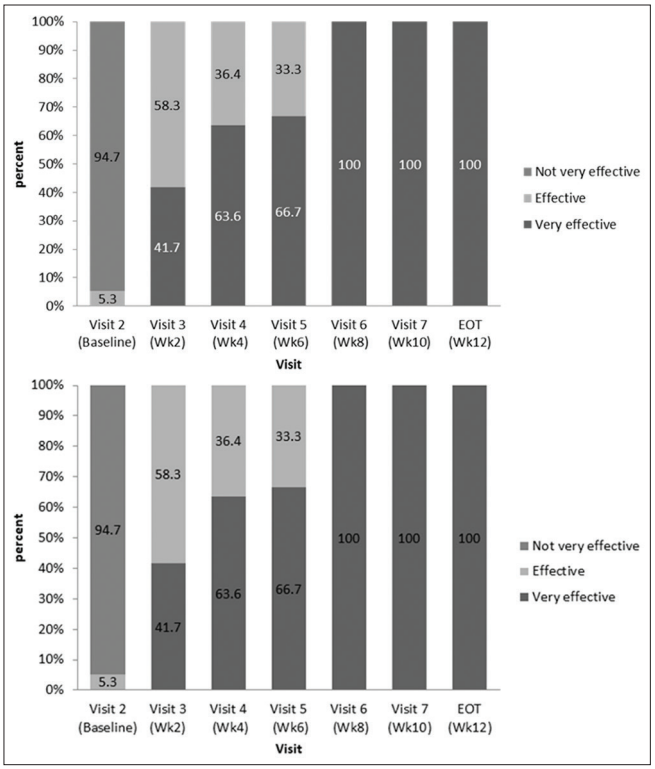

Figure 2: Patient satisfaction by using rate of quality of anesthesia. EOT: End of treatment

Table 2: Treatment-related adverse events during the whole study periods

Preferred term	*n* (%)
Musculoskeletal and connective tissue disorder	1 (1.8)
Joint swelling; joint tenderness	1
Blood and lymphatic system disorders	3 (5.4)
Anemia	3
Ear and labyrinth disorders	1
Vertigo	1
Gastrointestinal disorders	13 (23.20)
Constipation	1
Diarrhea	1
Hematochezia	2
Vomiting	3
Abdominal pain	1
Nausea	2
Stomatitis	3
General disorders and administration-site conditions	3 (5.4)
Edema peripheral	1
Mucosal inflammation	2
Infections and infestations	5 (5.4)
Sepsis	2
Pneumonia	1
Urinary tract infection	2
Injury, poisoning, and procedural complications	2 (3.6)
Sepsis	1
Wound complication	1
Investigations	2 (3.6)
Weight loss	2
Metabolism and nutrition disorders	10 (17.9)
Decreased appetite	3
Hypokalemia	5
Hyperkalemia	2
Musculoskeletal and connective tissue disorders	1 (1.8)
Muscular weakness	1
Nervous system disorders	4 (7.1)
Depressed level of consciousness	1
Dizziness	2
Headache	1
Psychiatric disorders	3 (5.4)
Insomnia	3
Respiratory, thoracic, and mediastinal disorders	3 (5.4)
Productive cough	2
Cough	1
Skin and subcutaneous tissue disorders	4 (7.1)
Decubitus ulcer	1
Alopecia	2
Palmar-plantar erythrodysesthesia syndrome	1
Cardiac disorder	1 (1.8)
Cardiac arrest	1

n: Numbers of patients who experienced the adverse events

Table 3: Time and average doses needed in the first stable titration (ITT population)

Variable / Status	ITT Population (*n*=19)
Time needs in first stable titration*	
n	13
Mean (SD)	4.2 (9.37)
Median (min, max)	1.0 (0, 32)
95% CI	(-1.43, 9.90)
Average dosage needs in first stable titration*	
n	13
Mean (SD)	20.8 (6.41)
Median (min, max)	20.0 (10, 40)
95% CI	(16.90, 24.64)

*Stable dose is defined as total daily dose is fixed for at least two weeks

Our analysis also showed that CR and IR oxycodone were effective in controlling the cancer pain in Taiwanese patients. The effectiveness appeared early within the first 2 weeks, where the NRS score had markedly decreased from 6.3 to 3.6 points. The therapeutic effect was also able to sustain continuously at a longer period to week 12, with the NRS score declining to 1.6 points. However, efficacy data vary between different studies. Bruera *et al*. demonstrated a stable pain intensity score,[17] with limited change across the study period, whereas Stambaugh *et al*. showed a remarkable improvement in pain control.[18] These differences may result from differences in patients' characteristics, disease severity, and the prescription/titration manner of oxycodone across countries.

Although our data demonstrated that 20-mg/day oxycodone was able to manage the cancer pain in 50% of patients, it also pointed out that 50% of the population was not getting enough pain control at this regimen. In our study, 81.2% of the patients who had pain intensity of NRS >3 (26/32; 32 patients with NRS >3 after receiving a stable dose of oxycodone) were prescribed with 20-mg/day oxycodone (data not shown). These findings indicated that physicians in Taiwan mostly took conservative approaches in titrating the dose of oxycodone, which may arise from the concerns of causing physical dependence. A more aggressive titration may be applied in the clinical practice for reaching an optimal dose for each patient.

The QoL assessment of oxycodone treatment was also performed using the EQ-5D-3L questionnaire in this study. Although EQ5D-3L VAS score showed varying data on the overall QoL, a detailed dimension analysis [Table 4] demonstrated that, even though the physical activities of those enrolled patients became worse, cancer pain treatment using CR and IR oxycodone improved their "anxiety/depression" and "pain/discomfort" items. As cancer pain has a significant impact on the overall quality of a cancer patient's life by influencing physical, psychological, and spiritual aspects,[19] our data proved again that a high-quality cancer pain treatment can really improve the emotional aspect of those cancer patients. There were some studies showed that the major reported QoL problems for colorectal cancer patients were "Pain/Discomfort" and "Usual activities" in a UK research,[20] while "Pain/Discomfort" and "Anxiety/Depression" were the major reported QoL problem in a Chinese research.[21] It seems that a certain consistency on the major reported QoL problems for colorectal cancer patients. As adequate cancer

Table 4: Numbers and proportion reporting levels within the European Quality of life-5 Dimensions: Pre- and post-treatments for moderate-to-severe cancer pain

EQ5D Item	Mobility		Self-Care		Usual Activities		Pain/Discomfort		Anxiety/Depression	
	Baseline	EOT	Baseline	EOT	Baseline	EOT	Baseline	EOT	Baseline	EOT
Level 1	14(70%)	8(42.1%)	16(80%)	11(57.9%)	11(55%)	10(52.7%)	0(0%)	4(21.1%)	0(0%)	13(68.4%)
Level 2	6(30%)	9(47.4%)	4(20%)	6(31.6%)	9(45%)	7(36.8%)	15(75%)	11(57.9%)	15(75%)	4(21.1%)
Level 3	0(0%)	2(10.5%)	0(0%)	2(10.5%)	0(0%)	2(10.5%)	5(25%)	4(21%)	5(25%)	2(10.5%)
Sum	20 (100%)	19(100%)	20 (100%)	19(100%)	20 (100%)	19(100%)	20 (100%)	19(100%)	20 (100%)	19(100%)
Patients with problems	6(30%)	11(57.9%)	4(20%)	8(42.1%)	9(45%)	9(47.3%)	20(100%)	15(78.9%)	20(100%)	6(31.6%)
No. difference of patients with problems	5		4		0		-5		-14	
% difference of patients with problems	26.30%		21.10%		0%		-26.30%		-73.70%	
Ranking of level change	5		4		3		2		1	

Level 1: Indicating no problems, Level 2: Some problems, Level 3: Extreme problems. Patients with problems indicating numbers (percentage) of Level 2 + Level 3. EOT: End of treatment, EQ5D: European Quality of Life-5 Dimensions

pain managements showed significant improvement on the 2 major reported problems, this may indicated that cancer pain may play an important role in the emotional aspects of colorectal cancer patients.

This single-center study showed the safety and tolerability of oxycodone as the primary outcome in Taiwan CRC patients. Unlike most studies investigating the effectiveness and tolerability of oxycodone in a short period of <30 days, our study provides a long-term safety and efficacy outcomes of oxycodone, as well as the associated QoL and patients' satisfaction.

However, this study has some limitations. During the 12-week study period, up to 75.3% of patients withdrew the study early, resulting in a median follow-up of 37 days (data not shown). It is likely that bias was introduced in the results of secondary end points due to the LOCF method used for replacing the missing data. Hence, the results must be interpreted with caution. Nevertheless, the data reflected an evidence that under no intervention of other opioid analgesic drugs, CR and IR oxycodone could help patients tolerate their cancer pain for 37 days on an average. A further potential limitation of the study is given by the open-label design, which may have resulted in a biased estimate of the study end points. It is possible that knowledge of the treatment received has systematically altered patient-reported outcomes because of likely differences in the way CR or IR oxycodone are perceived. However, this mirrors daily clinical practice more and the choice of the open-label design was also aimed at avoiding the complexity of blinding procedures which could interfere with the normal practice and decrease the number of patients enrolled.

Conclusion

CR and IR oxycodone were found tolerable and effective in managing moderate-to-severe cancer pain among patients with CRC cancers at the medical center. Neither new safety signals nor significant bowel function disorders were noted. Together with the high acceptability and improvements on anxiety/depression and pain/discomfort on Taiwanese cancer patients, it can be concluded that CR and IR oxycodone can be another valuable pain management option used for the daily control of moderate-to-severe cancer pain.

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Conflicts of interest

There are no conflicts of interest.

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