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Efficacy and Safety of High-Dose Controlled-Release Oxycodone in the Treatment of Moderate to Severe Pain in Patients with Advanced Cancer: A Retrospective Study

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Background: Opioid analgesics are used to relieve pain in patients with cancer and can improve their quality of life. This study aimed to investigate the efficacy and tolerability of high-dose (>150 mg/day) controlled-release oxycodone for the control of pain in patients with advanced solid malignant tumors.

Material/Methods: A retrospective clinical study was undertaken to include patients with advanced cancer treated at the Zhejiang Cancer Hospital who had treatment that included high-dose controlled-release oxycodone. The subjective numeric rating scale (NRS) for assessment of pain intensity (scores between 0–10) was used in all cases.

Results: The study included 131 patients with advanced solid tumors with moderate to severe cancer pain. The mean NRS score before commencing high-dose controlled-release oxycodone was 7.10. The effective rate of relief pain was achieved in 90.1% (118/131) of patients, with an average effective dose of controlled-release oxycodone of 177.18±11.71 mg/day, resulting in a mean NRS of 2.15. There were 51 patients who achieved pain relief with mean treatment duration of 49.98±11.71 days. Combination therapy was required in 79 patients. Additional drugs included gabapentin (43 patients), pregabalin (10 patients) and non-steroidal anti-inflammatory drugs (NSAIDs) (26 patients). The main side effects of high-dose controlled-release oxycodone included constipation, nausea, vomiting, dysuria, dizziness, and drowsiness, but no patients discontinued treatment because of these.

Conclusions: This study showed that high-dose controlled-release oxycodone could effectively relieve moderate to severe cancer pain, without side effects that were severe enough to result in discontinuation of treatment.

MeSH Keywords: **Drug-Related Side Effects and Adverse Reactions • Oxycodone • Pain Clinics**

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Background

In China, as life expectancy increases, the incidence of cancer and its associated morbidity and mortality have also increased [1]. Pain is one of the most common symptoms associated with cancer and as more patients present with advanced cancer with varying degrees of pain, this symptom is important to control to improve quality of life for patients. In a review published in 2008 on the prevalence of undertreatment of pain in patients with cancer, up to 75% of patients with advanced reported experiencing pain, and in approximately 50% of patients, the pain was moderate to severe [2]. The causes of pain in patients with cancer include the local effects of the tumor growth and local invasion, including to nerves and bone, the effects of therapy, and other complication of the tumor [2]. Recent clinical guidelines and recommendations on the management of patients with advanced cancer stress the importance of adequate pain relief with the use of opioid analgesics, to improve quality of life [3–5].

Controlled-release oxycodone is an opioid analgesic used for pain relief, which can be used orally every 12 hours, and is now widely accepted as an alternative to morphine, being as safe and effective as controlled-release morphine [6]. Oxycodone is an agonist of mu-opioid receptors in the brain and spinal cord and has some activity on kappa-opioid receptors, which are associated with pain perception, with some differences from morphine in its pharmacokinetics, in that oxycodone undergoes first phase metabolism via the CYP3A4 and CYP2D6 metabolic pathways [6–8]. Controlled-release oxycodone is a primary therapeutic drug and now accepted as an alternative to morphine in the treatment of moderate to severe cancer pain [8].

However, appropriate and effective management of cancer pain remains a significant issue for cancer pain patients. The use of high-dose controlled-release oxycodone (>150 mg/day) for cancer patients with advanced solid tumors has previously been reported to be effective and safe in some studies [9,10]. However, published evidence on the use of high-dose controlled-release oxycodone remains limited.

Therefore, the aim of this retrospective study at a single center was to investigate the efficacy and tolerability of high-dose (>150 mg/day) controlled-release oxycodone for the control of pain in patients with advanced solid malignant tumors.

Material and Methods

Patients studied

A retrospective review was undertaken of the clinical records of patients who were diagnosed with advanced solid tumors at

Zhejiang Cancer Hospital, China from March 2011 to December 2015. All patients included in the study had advanced-stage solid malignancy and underwent subjective numeric rating scale (NRS) for assessment of pain intensity (scores between 0–10), had a baseline NRS score of ≥ 4 and were able to take oral medication.

Demographic clinical data were collected on patient gender, age, type of cancer, drug treatments and pain characteristics. High-dose controlled-release oxycodone formulations were defined as oral treatment that would lead to a daily dose exceeding 150 mg when taken twice daily (every 12 hours). Patients were switched to high-dose controlled-release oxycodone with titration and monitored for at least two weeks. A baseline pain evaluation was carried out using the NRS scale, and the scale was used again to evaluate response to high-dose controlled-release oxycodone at follow-up. Previous medications used for pain relief were recorded.

Definition of patient response to treatment

In addition to the use of patient self-reported NRS scores, response to treatment was assessed using a modified World Health Organization (WHO) cancer pain ladder (www.who.int/cancer/palliative/painladder/en), which contained four levels: complete remission (CR) of pain; partial remission (PR) or reduction of the pain before the use of the drug, including an uninterrupted sleep pattern; minimal remission (MR) or reduction of the pain before the use of the drug but with pain severe enough to cause sleep interference; no change (NC), as the pain not changed from before the use of the drug.

An effective response rate to treatment was defined as (CR+PR)/all patients $\times 100\%$. The average duration of pain treatment varied depending on time in the patient's clinical course that high-dose controlled-release oxycodone treatment began and whether any dose adjustments were required.

Definition of adverse events associated with treatment for pain

Adverse events associated with treatment with high-dose controlled-release oxycodone, such as constipation, nausea, vomiting, dysuria, and respiratory depression were recorded from the patient records by incidence and severity. The severity of adverse effects was included as: mild (discomfort noticed, but no disruption in normal daily activities); moderate (discomfort sufficient to reduce or affect normal daily activities); or severe (causing inability to perform normal daily activities).

Table 1. Summary of patient characteristics at baseline (n=131).

Sex		Male		Female		
		80 (61.1%)		51 (38.9%)		
Age		Range (year)		Mean (year)		
		27~76		53		
Cancer	Lung	Liver	Colon	Breast	Stomach	Others
	61 (46.6%)	23 (7.6%)	12 (9.2%)	9 (6.9%)	7 (5.3%)	19 (14.5%)

Table 2. Summary of study findings after patients' switch from previous pain medication to high-dose oxycodone CR.

Number	Average NRS achieved	Average oxycodone CR dose	Average treatment duration (days)
131	2.15	177.18 mg/day	/
51	2.08	213.33 mg/day	49.98 d

Statistical analysis

Statistical analysis of data was performed using SPSS version 19.0 software. P-values ≤ 0.05 were considered statistically significant and the results were expressed as the mean $\pm$ standard deviation (SD).

Results

This retrospective study at a single center included 131 patients with advanced solid tumors with moderate to severe cancer pain. The patient population was 61.1% male (n=80) and 38.9% female (n=51). Patients were aged between 27–76 years (mean, 53 years). The following cancer diagnoses were made for the 131 patients: 46.6% lung cancer (n=61); 17.6% liver cancer (n=23); 10.13% prostate cancer (n=23); 6.9% breast cancer (n=9); 9.2% colon cancer (n=12); 5.3% stomach cancer (n=7); 0.8% esophageal cancer (n=1); 0.8% lymphoma (n=1); 0.8% cervical cancer (n=1); 0.8% ovarian cancer (n=1); 0.8% malignant thymoma (n=1); 0.8% bladder cancer (n=1); 0.8% nasopharyngeal carcinoma (n=1); and 0.8% osteosarcoma (n=1) (Table 1).

The overall numeric rating scale (NRS) score calculated for patients at the baseline was 5.44 before treatment with analgesic drugs. Of the 131 patients, 79.4% (104) reported moderate pain and 20.6% (27) reported severe pain. A range of pharmacological agents used before switching to high-dose controlled-release oxycodone: 70.23% were treated with low-dose controlled-release oxycodone; 7.63% were treated with low-dose controlled-release morphine; 9.16% were treated with transdermal fentanyl; 6.1% were treated with weak opioids; and 6.87% were treated with non-steroidal anti-inflammatory drugs (NSAIDs).

The mean NRS for patients before switching to high-dose controlled-release oxycodone with titration was 7.10. Pain control was achieved using an average dose of controlled-release oxycodone 177.18 $\pm$ 11.71 mg/day (range, 160–640 mg/day), resulting in an average NRS of 2.15. There were 51 patients on high-dose controlled-release oxycodone who were pain-free for an average treatment duration of 49.98 $\pm$ 11.71 days (Table 2). On high-dose controlled-release oxycodone, the effective rate of pain relief was 90.1% (118/131). Combination therapy was required in 79 patients. Additional drugs included gabapentin (43 patients), pregabalin (10 patients) and non-steroidal anti-inflammatory drugs (NSAIDs) (26 patients).

The main side effects of high-dose controlled-release oxycodone treatment included constipation, nausea, vomiting, dysuria, dizziness, drowsiness, pruritus, and respiratory depression, but no patients discontinued treatment because of these side effects. Mild and moderate constipation was reported in 63 patients (48.1%) and was controlled with laxatives. Nausea and vomiting were reported in 23 patients (17.6%). Dysuria was reported in 10 patients (7.6%). Drowsiness was reported in two patients (1.5%). Other adverse events including dizziness, pruritus, and respiratory depression in 4.6%, 1.5%, and 0.8% of patients, respectively (Table 3).

Comparison of the incidence of significant side effects (constipation, nausea and vomiting, dysuria) after the first week of use between controlled-release oxycodone and high-dose treatment are shown in Table 4, with significant differences between the groups: 35.9% vs. 48.1% (P<0.001); 23.7% vs. 17.6% (P<0.001); and 5.3% vs. 7.6%, (P<0.001). After treatment, the incidence of side effects in elderly patients was found to be lower than in younger patients, but no differences in pain levels were found (P>0.05) (Table 5).

Table 3. The adverse effects in all patients.

Side effects	n	Degree			Rate (%)
		Mild	Moderate	Severe	
Constipation	63	52	11	0	48.1%
Nausea and vomiting	23	18	5	0	17.6%
Dysuresia	10	9	1	0	7.6%
Dizziness	6	6	0	0	4.6%
Somnolence	2	2	0	0	1.5%
Skin itch	2	2	0	0	1.5%
Respiratory depression	1	1	0	0	0.8%

Table 4. Compare the incidence of major side effects (constipation, nausea and vomiting, dysuresia) after the first week of oxycodone CR with after high dose treatment.

Side effect	The first week		High-dose		P
Constipation	35.9%	(47/131)	48.1%	(63/131)	<0.001
Nausea and vomiting	23.7%	(31/131)	17.6%	(23/131)	<0.001
Dysuresia	5.3%	(6/131)	7.6%	(10/131)	<0.001

Table 5. The incidence of major adverse effects in elderly patients.

Side effect	Age ≥65 years		Age <65 years		P
Constipation	36.8%	(7/19)	50%	(56/112)	0.289
Nausea and vomiting	10.5%	(2/19)	18.8%	(21/112)	0.525
Dysuresia	5.3%	(1/19)	8.0%	(9/112)	1.000

Discussion

In China, there have been few studies on the effectiveness and safety of the use of high-dose controlled-release oxycodone in pain relief for patients with advanced cancer. Strong opioids are the primary treatments for moderate to severe cancer pain, and standard opioid treatment can relieve the pain of cancer in some patients [11]. However, there remains a group of patients with advanced cancer who achieve poor pain control with standard opioid therapy, and because of insufficient understanding of opioid use and availability, clinicians can be reluctant to use high-dose opioids due to the concerns regarding the side effects [12].

Morphine is considered the preferred drug to relieve pain in patients with cancer, due to its wide availability. [13]. However, oxycodone has been shown to be as effective and safe as morphine [14]. Oxycodone is the preferred drug to switch to when morphine fails to provide effective pain relief but could be recommended as a first-line drug for the control of moderate to

severe cancer pain [15]. A previously published 12-year study from Canada on high-dose opioid prescribing in patients with cancer showed that the prevalence of high-dose prescribing doubled (from 4.2% to 8.7%), and that 40.9% of recipients of long-acting opioids, exceeded daily doses of 200 mg morphine or equivalent, including 55.8% of users of long-acting oxycodone and 76.3% of users of transdermal fentanyl [16]. However, few reports have evaluated patients receiving high doses of controlled-release oxycodone. The findings of this retrospective study, performed in our center, showed the possible benefits of high-dose controlled-release oxycodone for pain control in patients with moderate to severe cancer pain, without increased side effects.

In the present study, before switching to high-dose controlled-release oxycodone, 70.23% of patients were treated with low-dose controlled-release oxycodone; 7.63% of patients were treated with low-dose controlled-release morphine; 9.16% of patients were treated with transdermal fentanyl; 6.1% of patients were treated with weak opioids; and 6.87% of patients

were treated with non-steroidal anti-inflammatory drugs (NSAIDs). In a previously published retrospective Italian study, 43% of patients were treated with low-dose oxycodone (either oxycodone/acetaminophen or controlled-release oxycodone); 30.0% of patients were treated with transdermal fentanyl; 12.8% of patients were treated with morphine; 5.3% of patients were treated with transdermal buprenorphine; 6.2% of patients were treated with weak opioids; and 1.3% of patients were treated with NSAIDs before treatment with high-dose controlled-release oxycodone [10]. Therefore, for some patients who do not have well-controlled cancer pain, importance should be given to the dynamic evaluation of cancer pain and treatment history, and individualized dose adjustments should be made in clinical practice. In the previously published study from Italy, the baseline NRS was 7.73 and using an average dose of controlled-release oxycodone of 221.84 mg/day the average NRS was reduced to 2.85 following a mean duration of therapy of 37.24 days [10].

In the present study, the subjective numeric rating scale (NRS) for assessment of pain intensity (scores between 0–10) was used in all cases. The mean NRS score before commencing high-dose controlled-release oxycodone was 7.10; the average effective dose of controlled-release oxycodone of 177.18 ± 11.71 mg/day resulted in a mean NRS of 2.15, and the effective rate of relief pain was 90.1% (118/131). In the present study, 51 patients attained pain relief on high-dose controlled-release oxycodone by a mean of 49.98 days. Therefore, high-dose controlled-release oxycodone could effectively relieve cancer pain within a relatively short period of time, which is more likely to have a positive effect on the quality of life of the patient with advanced cancer, as both an effective pain treatment and palliative treatment. Adequate pain relief was an important part of palliative treatment and optimal palliative care in cancer is associated with maximal pain relief. Also, the findings of this study showed that a history of combined drug use was present in 79 out of 131 patients, including gabapentin (43 patients), pregabalin (10 patients) and non-steroidal anti-inflammatory drugs (NSAIDs) (26 patients). As cancer progresses in each patient, the need for continued evaluation of pain and individual adjustment of pain medication dosing and drug combinations may be required.

Regarding the adverse effects of high-dose controlled-release oxycodone in cancer patients, the findings of this study showed that side effects were common but not severe and included constipation, nausea, vomiting, and dysuria. Constipation is a common side effect of opioid use, and patients do not usually develop tolerance to constipation during treatment [11]. In our study, constipation occurred in 63 patients (48.1%) and was not severe enough to discontinue the use of oxycodone. In this study, the incidence of constipation was compared after the first week of controlled-release oxycodone and after high-dose treatment and found significant differences (35.9% vs. 48.1%) ($P < 0.001$). Although constipation can be controlled with laxatives, constipation should be monitored in patients treated with high-dose controlled-release oxycodone. Nausea and vomiting occurred in 23 patients (17.6%) but declined after high-dose treatment comparing with the first week of treatment (23.7% vs. 17.6%) ($P < 0.001$). Dysuria occurred in 10 patients (7.6%), and the incidence increased in the high-dose treatment group (5.3% vs. 7.6%) ($P < 0.001$). There were no significant differences in the incidence of side effects of nausea, vomiting, constipation, or dysuria between elderly patients and younger patients.

The findings of this retrospective clinical study conducted at a single center showed that high-dose controlled-release oxycodone could effectively relieve moderate to severe cancer pain, without side effects that were severe enough to result in discontinuation of treatment.

The main limitations of this study were the retrospective analysis, which was dependent on the quality of the patient records, and the small study sample size, particularly for elderly patients.

Conclusions

High-dose controlled-release oxycodone is a safe and appropriate treatment for the control of moderate to severe pain in patients with advanced cancer. However, further randomized studies involving high-dose controlled-release oxycodone are required to support the findings of this preliminary retrospective study that also include a larger proportion of elderly patients with advanced cancer.

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