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Early introduction of intravenous oxycodone injection followed by quick titration to oral oxycodone in outpatient cancer pain treatment in opioid-naïve patients: "oxycodone bridge method"

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ABSTRACT

Following opioid therapy initiation in opioid-naïve outpatients, cancer-related pain does not improve immediately, and pain relief is maintained after many days. This prospective study aimed to evaluate the feasibility of quick opioid introduction with injectable oxycodone for outpatient cancer-related pain and bridge to oral persistent-release tablet. Patients with Numerical Rating Scale of ≥4 for cancer-related pain were included. Injectable oxycodone 2 mg was evaluated for efficacy and safety after 30 min of administration; in case of lower efficacy, injectable oxycodone was administered for another 30 min. For patients exhibiting improvement 30 and 60 min after injectable oxycodone administration, oral persistent-release tablet 5 and 10 mg were initiated, respectively. If side effects are acceptable, oral persistent-release tablet twice daily was prescribed. The final evaluation for its efficacy and safety was conducted at revisit. Overall satisfaction (1–5 points, higher points are better) was evaluated. The study included 23 patients (26 symptoms). The Numerical Rating Scale was improved from 6.7 ± 1.9 to 2.5 ± 2.5 and 1.3 ± 1.3 at 30 min after injectable oxycodone and revisit, respectively. Five patients with six symptoms receiving 60 min of injectable oxycodone had Numerical Rating Scale of 3.7 ± 1.7 and 1.7 ± 1.2 at revisit. No patient had Grade 3 or higher side effect during injectable oxycodone and at revisit. The overall satisfaction was 4.4 ± 0.8. In conclusion, early injectable oxycodone introduction for opioid-naïve outpatients can be feasible and useful as a quick bridge to oral persistent-release tablet.

Keywords: opioid-naïve, cancer-related pain, opioid titration

Abbreviations:
IO: injectable oxycodone
NRS: Numerical Rating Scale
OT: oral persistent-release tablet

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INTRODUCTION

When initiating opioids in opioid-naïve patients, a safe starting dose of oral medication must be administered, and response must be monitored over several days. Therefore, sufficient pain improvement is not always achieved promptly. On the contrary, injectable medications, if administered in appropriate doses, can produce a rapid effect. Guidelines have established a system for converting the daily dose of intravenous injections into the required oral dose; however, none has recommended converting the daily dose in as short a time as a few hours.[1]

Since 2013, our clinic has been treating patients at the time of opioid induction from a small intravenous dose of oxycodone in an outpatient setting to initiate prompt bridging to oral therapy.

This study aimed to estimate the feasibility of early opioid introduction using injectable oxycodone (IO) for outpatient cancer-related pain and as an immediate bridge to optimal oral formulations.

IO showed dose linearity between the dose rate and plasma concentration during the continuous injection.[2] For example, if the drip speed doubled, the slope of the time–concentration line also doubled. For the daily dose of oxycodone oral persistent-release tablet (OT) in the study of patients with cancer, the maximum plasma concentration of 20 mg (10 mg twice a day) tablet has been reported to range from 17 ± 4.7 to 23.2 ± 8.6 ng/mL.[3,4] Its median is approximately 20 ng/mL. According to the continuous injection model, continuous IO by 1 mg/h becomes 5 ng/mL in 1 h in plasma concentration.[5] To reach the maximum plasma concentration of 20 ng/mL with continuous IO corresponding to daily OT 20 mg (10 mg twice daily), the plasma concentration in 1 h with continuous IO requires increasing the injecting dose rate to approximately four times, which results in 4 mg/h according to its dose linearity.[2] As for a 30-min drip with the same speed, it becomes approximately 10 ng/mL in plasma concentration, which is assumed as a plasma concentration of steady state of daily 10 mg (5 mg administered twice daily) OT.

The original pain ladder of the World Health Organization for opioid-naïve patients recommended the use of oxycodone, a strong opioid, following a weak opioid therapy. Currently, a low-dose therapy of a strong opioid proved to be reliable in titrating opioid-naïve patients rather than the use of a weak opioid.[6,7] However, there is no solid evidence to indicate that the initial dose of strong opioids that can be properly controlled. It has only been reported that opioids should be initiated at the lowest possible dose to achieve acceptable analgesia and patient goals, with early assessment and frequent titration.[1,8] Practically, since OT 5 mg is on the market[5] since 2003, we have been using OT to opioid-naïve patients. Therefore, the starting dose is a low-dose oxycodone, ie, OT 5 mg twice a day. However, while moderate pain[9,10] with a Numerical Rating Scale (NRS) of 4–6 can be covered with OT 5 mg (10 mg/day), severe pain[10] with an NRS of 7 or more requires treatment with a high dose of OT 10 mg (20 mg/day). In this study, the first 30 minutes of IO was equivalent to OT 10 mg/day while another 30 minutes of IO was equivalent to OT 20 mg/day. It was determined that, to some extent, OT 20 mg could be used for the treatment of cases of severe pain with an NRS of 7 or more. Based on these findings, it was suggested that if the indication for starting opioids is for cases with an NRS of 4 or more, it can be used to treat almost all opioid-naïve patients. Moreover, the half-life of a bolus injection of oxycodone is 2–3 h.[5] The time to maximum concentration of OT is approximately 2.6 h.[3] If the abovementioned OT is administered after IO to have seamless pain control with oxycodone, the expected peak plasma concentration time could be within 3 h after the end of the drip infusion. Thus, if a single oral formulation was switched from IO in the outpatient setting, approximately 3 h of observation may be enough to evaluate its efficacy and adverse events. Accordingly, a planned protocol treatment was made (Fig. 1) to bridge from IO to OT and evaluate the success and adverse effects of IO and OT.

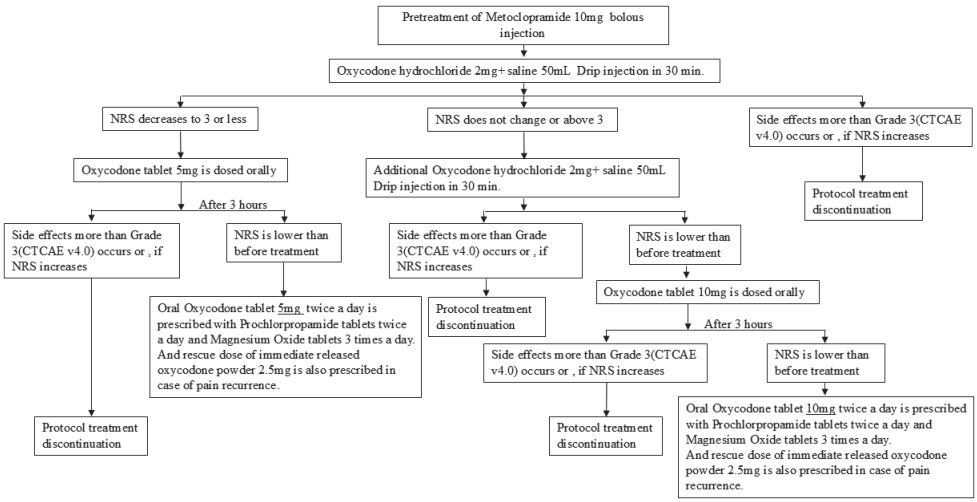

Fig. 1 Protocol treatment

After pretreatment with metoclopramide, 2 mg injectable oxycodone was infused for 30 min. If the NRS decreased by ≤3, oxycodone tablet 5 mg was administered. The patient was allowed to go home after 3 h of observation. If the NRS decreased but did not fall below 3, an additional infusion of 2 mg of oxycodone was given for 30 min, for a total of 60 min.

If there was no worsening of pain regardless of the NRS falling below 3, the patient was given 10 mg of oxycodone tablets and sent home after 3 h of observation if there are no problems. Treatment was discontinued if there are serious (grade ≥3) adverse events throughout the protocol treatment or if there was no effect on pain at all.

CTCAE ver4.0: NCI Common Terminology Criteria for Adverse Events version 4.0.

NRS: Numerical Rating Scale

MATERIALS AND METHODS

Participants

In outpatients with cancer-related pain that could not be controlled by nonopioid treatment and met the eligibility and exclusion criteria (Table 1), early introduction of IO was assessed.

Table 1 Eligibility and exclusion criteria of the study

Eligibility criteria
• Opioid-naïve
• Suffering from NRS 4 or more cancer related pain in spite of NSAIDs and/or acetaminophen dosage
• Age>18 year old
• Estimated survival at least 1 month
• Absence of cognitive impairment or psychiatric illness
• Performance Status 0 or 1 (except for patients with bone metastases)
Exclusion criteria
• Opium alkaloid allergy
• Severe hepatic or respiratory failure
• Inability to tale oral medications
• Radiation therapy was performed two weeks before the test day

NRS: Numerical Rating Scale

NSAIDs: nonsteroidal anti-inflammatory drugs

Opioid-naïve patients who had moderate or severe cancer-related pain with a NRS score of ≥4 despite intake of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen, were aged >18 years, had estimated survival for at least 1 month, had no cognitive impairment or psychiatric illness, and had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≤2 were included.[11] If patients had concomitant pains of different types and if each pain is present at different sites and can be assessed separately, each pain is tested independently. Patients who had opium alkaloid allergy, severe hepatic and respiratory failure, inability to take oral medications, and radiation therapy 2 weeks before the treatment day were excluded (Table 1).

Measurements

The primary endpoints included the efficacy and titration potential of IO. Titration potential was defined as successful bridging from IO to OT. Thus, it was assessed[9,10] as "appropriate" if no dose modification was needed at revisit and the NRS score for pain was ≤4 and "optimal" if the NRS score was ≤3.

The secondary endpoint was safety. This was assessed based on side effects observed after IO and at revisit after bridging to OT. All side effects were graded from 1 to 5 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events[12] version 4.0. A severe side effect was defined as graded ≥3.

Protocol treatment

After the drip infusion of metoclopramide 10 mg as a prophylactic drug for opioid-induced emesis, 2 mg IO in 50 mL of saline was infused in 30 min. The first assessment was done after 30 min. If the patient's NRS decreased to <4, the regimen was defined as effective. If the effect was small, the NRS score was not below 4, and side effects of grade ≤2 were observed, the same evaluation was performed following infusion of another 2 mg IO in 50 mL of saline until a total period of 60 min. If the 30-min infusion protocol was invalid or whenever grade ≥3 side effects were observed, the protocol was discontinued. For patients exhibiting improvement after the first 30 min of infusion, OT 5 mg was administered, and for those with improvement of any extent after 60 min of infusion, OT 10 mg was administered after IO. Meanwhile, if the 60-min infusion protocol was invalid or grade ≥3 side effects were observed, this protocol was discontinued. Then, to assess other adverse events, observations were made 3 h after successful completion of both IO and OT. If these side effects (grade ≤3) can be tolerated, each dose of OT twice daily was prescribed with supportive drugs such as prochlorpropamide and magnesium oxide. Then, patients were allowed to go home. The final assessment of its safety and efficacy was made at the next visit (the revisit) within a couple of days (Fig. 1). Rescue doses were prescribed as 2.5 mg immediate-release OT of oxycodone. The rescue dose was expressed as the maximum number daily until the revisit. Overall satisfaction of the patient's subjective assessment (1–5 points: 1. Dissatisfied; 2. Somewhat dissatisfied; 3. Average; 4. Somewhat satisfied; 5. Satisfied) was also assessed at the end of all treatment protocols.

After obtaining the approval of the local ethics committee of the Toyohashi Municipal Hospital in May 2013, the study was performed with patients' consent from November 2013 to December 2019.

Statistical analysis

Continuous variables were expressed as means ± standard deviations. To assess the significance of changes in data, the Wilcoxon signed-rank test was used to compare each of the two datasets to assess whether the overall change was constant. Statistical analysis was performed using R version 4.2.2 (R foundation for Statistical Computing, Vienna, Austria). All data evaluations were

considered changed significantly when the P-value was <0.05.

RESULTS

Consecutive 44 patients who attended the outpatient clinic of the general surgery of Toyohashi Municipal Hospital between June 2013 and December 2019 were identified. Of these 44 patients, 19 patients did not consent after explanation of this protocol. The remaining 25 patients were eligible and consented; however, 2 of the 25 patients were excluded because they were hospitalized immediately with psychological problems and declined to continue this protocol. Finally, 23 patients were enrolled in this study. The median age was 66 (54–79) years, and the median PS was 1 (0–2). Underlying diseases included colorectal cancers (n = 9), breast cancers (n = 7), pancreatic cancers (n = 4), duodenal cancer (n = 1), gastrointestinal stromal tumor (GIST) of the small intestine (n = 1), and gastric cancer (n = 1). Two patients had comorbid diseases such as lumbar spinal canal stenosis, chronic kidney disease, and hypertension. Concomitant pain drugs were NSAIDs in 21 patients, acetaminophen in 6, and pregabalin in 2. Diuretics and sleep-inducing drugs were prescribed in one patient. Ten patients received the best supportive care, and the remaining 13 patients had their first to eight lines of chemotherapy. Moreover, 26 totally different metastatic site pains were noted, and a patient had three overlapping pains. Of the 26 sites, 12 were noted in the peritoneum (one overlapping), 6 in the bones (one overlapping), 4 in the lymph nodes (one overlapping), 1 in the pleura (one overlapping), 1 in the sacral nerve plexus, 1 in the celiac nerve plexus, and 1 in the axillary nerve (one overlapping). The 26 pain sites included 12 for the abdomen (one overlapping), 4 for the lower back, 3 for the chest (two overlapping), 3 for the axilla (two overlapping), 1 for the lower extremities, 1 for the right leg, 1 for the right arm (one overlapping), and 1 for the whole body. The nature of cancer pains was 16 visceral pains (two overlapping), five neuropathic pains (one overlapping), and five bone-related pains (one overlapping). Post-treatment prognoses were 8.4 ± 12.4 (1–45) months (Table 2).

The NRS score improved from 6.7 ± 1.9 (4–10) at the start of the study to 2.5 ± 2.5 (0–10) after 30 min of IO.

The NRS score at revisit was 1.3 ± 1.3 (0–4), and no exacerbation was noted. The 30-min treatment protocol was finished in 18 of these samples (16 cases). Their NRS scores improved significantly from 6 ± 1.7 at baseline, 1.1 ± 1.1 at 30 min, and 1.1 ± 1.3 at revisit (Fig. 2a). The remaining eight samples (seven cases) required an additional 30 min of IO (until 60 min), which eventually improved. All these eight samples improved significantly from 8.1 ± 1.5 at baseline, 5.5 ± 2.1 at 30 min, 3 ± 1.9 at 60 min, and 1.8 ± 1.2 at revisit. The proportion of the determined appropriate titration potential of 30-min IO to 5 mg OT was 100% (18 of 18 samples). Its optimal titration potential was 94% (17 of 18 samples; Fig. 2a). In samples with 60 min IO titrated to 10 mg OT, the titration potential was appropriate in 100% (8 of 8 samples) and optimal in 100% (8 of 8 samples; Fig. 2b).

Table 2 Patients' background

	Age	Gender	PS	Malignant disease	Current state	Comorbid disease	NSAIDs	Acetamino-phen	Additional analgesic drug	Painful metastatic site	Site of pain	Nature of pain	Postprotocol prognosis (month)
Case 1	67	M	2	Pancreatic Ca	BSC		+	–		Peritoneum	Abdomen	Visc	2
Case 2	62	F	2	Pancreatic Ca	Chemo 1st line		+	–		Peritoneum	Abdomen	Visc	1
Case 3	70	F	0	Colorectal Ca	Chemo 3rd line		+	+		Peritoneum	Abdomen	Visc	3
Case 4	79	M	2	Duodenal Ca	BSC	Lumbar spinal canal stenosis	+	–		Peritoneum	Abdomen	Visc	1
Case 5	65	M	2	Colorectal Ca	Chemo 4th line		+	+	Pregabalin	Sacral plexus	Lower extremity	Neuro	5
Case 6	67	M	0	Colorectal Ca	BSC		+	–		Peritoneum	Abdomen	Visc	7
Case 7	72	F	1	Colorectal Ca	Chemo 2nd line		+	–	Pregabalin	Peritoneum	Abdomen	Visc	2
Case 8	66	M	0	Colorectal Ca	BSC		+	–		Peritoneum	Abdomen	Visc	3
Case 9	65	M	0	Colorectal Ca	Chemo 3rd line		+	–		Peritoneum	Abdomen	Visc	15
Case 10-a	54	F	2	Colorectal Ca	BSC	Chronic kidney disease, Hypertension	+	–		Pleura	Chest	Visc	1
Case 10-b							+	–		Peritoneum	Abdomen	Visc	
Case 11	66	M	1	Intestinal GIST	Chemo 2nd line		+	–		Peritoneum	Abdomen	Visc	1
Case 12	69	F	2	Breast Ca	BSC		+	–		Systemic bone	Whole body	Osteo	6
Case 13	70	F	2	Breast Ca	Chemo 8th line		–	–	Tramset	Right femur bone	Right leg	Osteo	1.5
Case 14	71	F	0	Colorectal Ca	Chemo 1st line		+	–		Costal bone	Chest	Neuro	13
Case 15	72	F	0	Breast Ca	Chemo 5th line		+	–		Axillar LN	Axilla	Visc	1.5
Case 16-a	73	F	0	Breast Ca	Chemo 1st line		+	–		Axillar LN	Axilla	Visc	45 (alive)
Case 16-b							+	–		Costal bone	Chest	Osteo	
Case 17-a	57	F	0	Breast Ca	Chemo 1st line		+	–	Pregabalin	Axillar LN	Axilla	Visc	10
Case 17-b							+	–		Axillar N plexus	Right arm	Neuro	
Case 18	66	M	0	Gastric Ca	BSC		–	–	Tramset	Aortic LN	Low back	Neuro	2
Case 19	30	F	2	Breast Ca	Chemo 1st line		+	–		Spinal bone	Low back	Osteo	34 (alive)
Case 20	39	F	1	Breast Ca	Chemo 1st line		+	–		Spinal bone	Low back	Osteo	34 (alive)
Case 21	70	F	1	Colorectal Ca	BSC		+	–		Peritoneum	Abdomen	Visc	1.5
Case 22	63	M	2	Pancreatic Ca	BSC		+	–		Celiac plexus	Low back	Neuro	2
Case 23	69	M	1	Pancreatic Ca	BSC		+	–		Peritoneum	Abdomen	Visc	1

BSC: best supportive care
Ca: carcinoma
Chemo: chemotherapy
GIST: gastrointestinal stromal tumor
LN: lymph node
Neuro: neurogenic pain
NSAIDs: nonsteroidal anti-inflammatory drugs
Osteo: osteogenic pain
PS: Performance Status
Tramacet: paracetamol and tramadol hydrochloride
Visc: visceral pain

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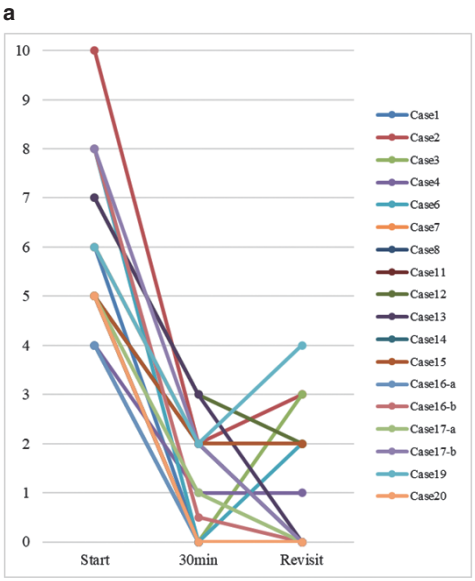
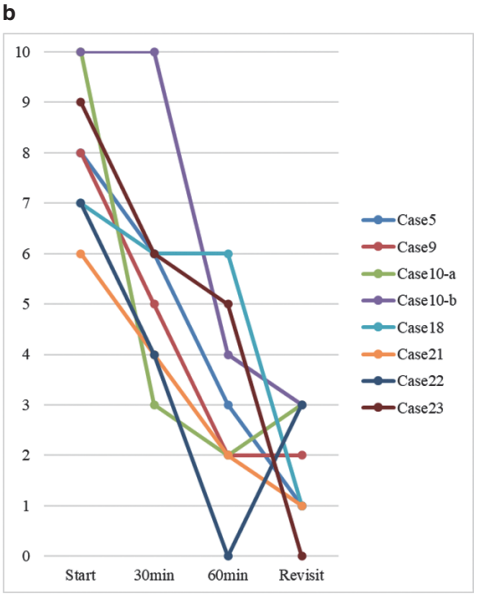


	Start	30min	Revisit
Case1	6	0	0
Case2	10	2	3
Case3	5	0	3
Case4	4	1	1
Case6	8	0	2
Case7	6	2	2
Case8	5	2	0
Case11	5	0	0
Case12	7	3	2
Case13	7	3	0
Case14	4	0	0
Case15	5	2	2
Case16-a	4	0	0
Case16-b	8	0.5	0
Case17-a	5	1	0
Case17-b	8	2	0
Case19	6	2	4
Case20	5	0	0

$ p= 0.000191* $ p=0.877 $ p= 0.000204*



	Start	30min	60min	Revisit
Case5	8	6	3	1
Case9	8	5	2	2
Case10-a	10	3	2	3
Case10-b	10	10	4	3
Case18	7	6	6	1
Case21	6	4	2	1
Case22	7	4	0	3
Case23	9	6	5	0

$ p = 0.0213* $ p= 0.022* $ p = 0.268 $ P = 0.0137*

Fig. 2 Changes in pain NRS after treatment

Fig. 2a: Change of each case in pain NRS for the 30-min IO group. The pain NRS score significantly decreased from the start to 30 min and to revisit. $, Wilcoxon signed-rank test, was used to compare each of the two datasets assessing whether the overall change was constant. * P < 0.05, which was assessed as statistically significant.

Fig. 2b: Change of each case in pain NRS for the 60-min IO group. The pain NRS score significantly decreased from the start to 30 min and to revisit. Moreover, it significantly decreased from 30 min to 60 min and from 60 min to revisit. $, Wilcoxon signed-rank test, was used to compare each of the two datasets assessing whether the overall change was constant. * P <0.05, which was assessed as statistically significant.

NRS: Numerical Rating Scale

IO: injectable oxycodone

The side effects of IO were noted in 9 (39%) patients (five patients with grade 1 somnolence and four with grade 1 nausea). Six of nine symptoms spontaneously disappeared. As for the three remaining symptoms, patients did not feel discomfort and did not require further treatment (Table 3). After 3 h from OT administration following IO, no symptom or augmentation of previous symptoms occurred. All patients were allowed to go home after the first day of the treatment protocol.

Table 3 Adverse effect after oxycodone injection

	Adverse effect	Grade #	Management
Case 1	Nausea	1	Spontaneously disappeared soon
Case 2	Somnolence	1	Spontaneously disappeared soon
Case 3	0		
Case 4	0		
Case 5	0		
Case 6	Somnolence	1	Spontaneously disappeared soon
Case 7	0		
Case 8	0		
Case 9	0		
Case 10	Somnolence	1	Patients didn't want any treatment
Case 11	0		
Case 12	0		
Case 13	0		
Case 14	Somnolence	1	Patients didn't want any treatment
Case 15	0		
Case 16	Somnolence	1	Patients didn't want any treatment
Case 17	0		
Case 18	Nausea	1	Spontaneously disappeared soon
Case 19	0		
Case 20	Nausea	1	Spontaneously disappeared soon
Case 21	Nausea	1	Spontaneously disappeared soon
Case 22	0		
Case 23	0		

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events' Grade

At revisits, four grade 1 side effects (three patients with somnolence and one with headache) and seven grade 2 side effects (three patients with constipation, two with floating sensations, one with dysuria, and one with nausea) were recorded. Three of five grade 1 side effects did not need further management. One patient who suffered a grade 2 dysuria required dose reduction of oxycodone. Two patients who had grade 2 floating sensations and one patient who had nausea changed their antiemetic drug from prochlorperazine to diphenhydramine for symptom control. Constipation cases were all successfully treated with lubiprostone instead of magnesium oxide (Table 4).

Table 4 Adverse effect after final visit

	Adverse effect	Grade #	Management
Case 1	Headache	1	Patient didn't want any treatment
Case 2	Somnolence	1	Patient didn't want any treatment
Case 3	Floating sensation	2	Prochlorperadine→Diphenhydramine
Case 4	Somnolence	1	Patient didn't want any treatment
Case 5	Dysuria	2	Reduction of oxycodone tablets
Case 6	Constipation	2	Magnesium oxide→Rubiprostone
Case 7	Somnolence, Constipation	1, 2	Magnesium oxide→Rubiprostone
Case 8	0		
Case 9	0		
Case 10	Constipation	2	Magnesium oxide→Rubiprostone
Case 11	0		
Case 12	0		
Case 13	Nausea	2	Prochlorperadine→Diphenhydramine
Case 14	Floating sensation	2	Prochlorperadine→Diphenhydramine
Case 15	0		
Case 16	0		
Case 17	0		
Case 18	0		
Case 19	0		
Case 20	0		
Case 21	Nausea	2	
Case 22	0		

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events' Grade

Rescue doses were taken for 9 of 26 symptoms (27%). Rescue doses were also taken for six of nine symptoms because of breakthrough pain and for inadequate pain control of the persistent pain. Two of these nine symptoms were neuropathic pain, and the rest was visceral pain. The maximum number of daily rescue doses varied 0 to 4 (1.5 ± 1.8; Table 5). Finally, daily doses of oxycodone were modified for two symptoms (7.7%): one needed dose augmentation, and another needed reduction because of dysuria (Table 4). Finally, the overall satisfaction score of the patient was 4.3 ± 0.7 (2–5). Most patients had satisfaction scores of ≥4, except for patients 2, 5, and 18 (Fig. 3).

Table 5 Times of rescue doses

	Maximum numbers of times per day of rescue doses
Case 1	4
Case 2	4
Case 3	0
Case 4	0
Case 5	2
Case 6	5
Case 7	3
Case 8	0
Case 9	3
Case 10	0
Case 11	0
Case 12	4
Case 13	0
Case 14	0
Case 15	3
Case 16	0
Case 17	0
Case 18	4
Case 19	0
Case 20	0
Case 21	0
Case 22	2
Case 23	0
Mean	1.5 ± 1.8, range 0–5

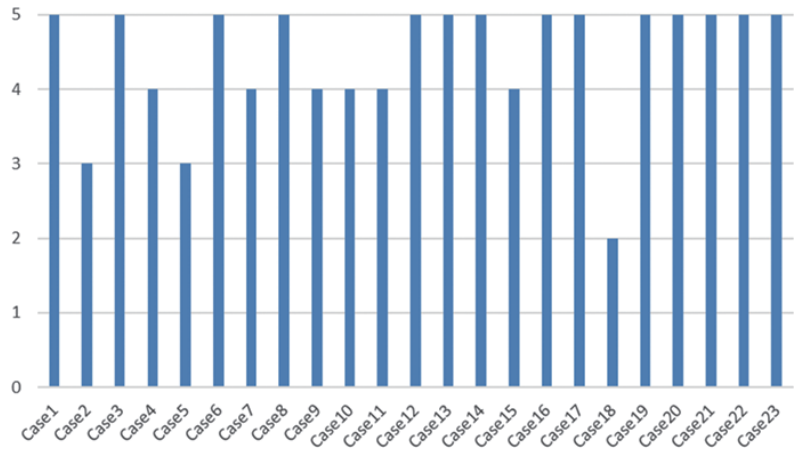


Fig. 3 Overall satisfaction of the patient's subjective assessment
It was scored 1–5 points (higher scores indicated better overall satisfaction). The mean was 4.3 ± 0.7, with a range of 2–5, and no patient rated 1.

DISCUSSION

In this study, cancer-related pain of NRS ≥4 in opioid-naïve outpatients improved promptly with small amount of IO for 30–60 min, which was further switched to OT. The appropriate and optimal titration potentials of the 30-min IO to 5 mg OT were 100% and 94%, respectively. Moreover, the titration potentials of the 60-min IO to 10 mg OT were also 100%. This ultimately helped to determine whether the minimum starting dose of strong opioids for patients with cancer-related pain is 10 mg per day or ≥20 mg is required.

However, one patient had a mild exacerbation with an NRS score of 4 when he returned to our clinic, and some issues remained to be addressed, such as severe pain that does not reach an NRS score of <4 even after 60 min of IO and patients who have been rescued >4 or 5 times per day.

Adverse reactions to oxycodone were reported in 30%–60% of cases, and serious reactions leading to discontinuation were in approximately 2.5% of cases.[13] In this study, our data were clearly below these levels and were considered safely administered.

Both oral and intravenous opioid inductions are recommended for opioid-naïve patients with moderate to severe cancer-related pain and an NRS score of ≥4. The times to maximum therapeutic effect for immediate release of oral and intravenous medications are 60 and 15 min, respectively.[1,3] Based on these considerations, the intravenous route is the preferred choice for patients with severe pain. However, in the outpatient setting, immediate-release formulations of oral opioids are often chosen because of their simplicity.[1,3,14-16]

Whether with intravenous or oral administration, the key is to confirm the effect as soon as possible and to achieve a sustained effect. When palliative treatment is given as an outpatient rather than as an inpatient treatment and the first opioid is administered, the effectiveness of pain improvement will often be confirmed at the next outpatient visit, ie, a few days to a week later. If no improvement or strong side effects were noted after the initial administration, a major delay in palliative treatment is possible. Recently, a 12-h opioid titration method has been reported.[17] Although this method may have significantly reduced the number of days of evidence to date, patients can remain in pain for the first 12 h. Conversely, induction by intravenous infusion in an inpatient setting is safe and secure for many pain sufferers. Guidelines suggest that rapid intravenous opioid infusion should be administered first to confirm efficacy, the dose to be given over 24 h should be established empirically, and the daily oral requirement should be determined from the total dose and efficacy after 24 h, with repeated rescue doses. This method may provide rapid analgesia; however, whether it will provide a rapid and sustained effect is uncertain. Therefore, the transition to oral therapy is not possible until at least the next day, and in some cases, it may take several days.

To solve the above two problems, namely the rapid induction and rapid acquisition of effective maintenance doses of opioid, in our study, the efficacy and side effects on pain were observed for 1 h in an outpatient setting, and the theoretically necessary amount of extended-release OT was determined and administered based on the amount of IO administered. The efficacy and side effects were then checked several days later. The conclusion was reached a few days later; although initially, it appears to be no different from the usual outpatient and inpatient methods described above, the effects being confirmed promptly in the outpatient setting was significant, and the quality of life was considered higher than that with inpatient treatment because patients did not require admission. This is evidenced by the high patient satisfaction score of 4.2 on a 5-point scale.

Note that this study has several limitations. First, this study was based on a small number of patients and had weak statistical power. Further case accumulation is needed if a definitive

formulation is needed. However, as with other forms of palliation, all treatments in palliative medicine can be tried and tested; thus, the clinical problem is no longer a problem as long as symptoms are relieved and the patient is followed up within a few days.

Second, whether this protocol addresses all pain types in outpatient opioid-naïve patients is unclear: for moderate or higher pain with an NRS score of ≥4, the mean was 6.7 ± 1.9, with 12 cases (46%) having pain of ≥7. Some cases had an NRS of 3 at 30 min after injection but increased again to 4 when switched to OT (Fig. 2a), and others required rescue doses five times a day (Table 5). A 60-min intravenous infusion of 4 mg oxycodone may not be sufficient or may require more fine-tuning for breakthrough pain or pain at the end of opioid withdrawal.[1,18] However, the initial oxycodone dosage for opioid-naïve outpatients is no different from the current outpatient setting, with a minimum dose of 10 or 20 mg per day.[13] In this study, we believe that the minimum dose of 10 mg was sufficient for many patients and that the clinical value of the study was sufficient to select the population that would need up to 20 mg on top of that.

Third, although the results were satisfactory for the patients, the scale adopted in the study was not validated and subjective that could not determine the aspects of satisfaction of patients. The results of the general patient satisfaction survey, conducted in 2019 for our entire hospital and department of general surgery, was taken as reference and the outcomes were 3.8 and 3.1, respectively. Therefore, the value of 4.2 in this study was presumed to be higher than that of general patients.

If we do not know whether it is pain or quality of life, it is impossible to determine the direction of improvement. We had the data of the survey as our hospital conducts such satisfaction surveys for all palliative treatments; however, it would have been more beneficial if a detailed quality of life survey had been conducted in this study.

CONCLUSIONS

The early introduction of IO for opioid-naïve outpatients might be feasible and used as a quick bridge to OT in the outpatient setting.

DISCLOSURE STATEMENT

The authors declare no competing financial interests.

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