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ORIGINAL ARTICLE

A prospective, open-label, multicenter study of the clinical efficacy of extended-release hydromorphone in treating cancer pain inadequately controlled by other analgesics

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Abstract
Purpose The objective of this study was to evaluate whether extended-release hydromorphone (osmotic-controlled release oral delivery system [OROS] hydromorphone) treatment provided pain relief in cancer patients whose pain was inadequately controlled by other analgesics.
Methods In this prospective, open-label, multicenter trial, patients who have sustained cancer pain with other analgesics

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were enrolled. After the baseline evaluation (visit 1), OROS hydromorphone was administered. Two evaluations (visits 2 and 3) were made: 29±7 and 57±7 days later, respectively. The primary end point was the pain intensity difference (PID) at visit 3 relative to visit 1 (expressed as percent PID).
Results In total, 879 patients were screened and 432 completed all three visits. Of the 874 full analysis set patients, 343 (39.2 %) improved by more than 30 % PID. Of the 432 per-protocol patients, 282 (65.3 %) improved by more than 30 % PID. At visits 2 and 3, the degree of sleep disturbance, the number of awakenings, and the degree of sleep satisfaction were significantly better than at visit 1 (all $P<0.0001$ for both visit 1–visit 2 and visit 1–visit 3). However, this pain relief was not associated with improved quality of life ($P=0.326$ and $P=0.055$ for visit 1–visit 2 and visit 1–visit 3, respectively).
Conclusions This study suggested that active pain management using the strong opioid OROS hydromorphone was beneficial in the management of cancer pain that was not controlled by other analgesics.

Keywords Analgesics · Cancer · Hydromorphone · Opioid · Pain

Introduction

Pain management is an important component of cancer treatment during all phases of cancer. The means and knowledge to relieve most cancer pain are available, but surveys and observational studies have shown that many patients still have troublesome or severe pain and do not get adequate relief [1–5]. This undertreatment is usually attributed to the inappropriate use of opioids. In a recent Korean survey in physicians, only 16.5 % of respondents stated that they would prescribe strong opioids in response to a hypothetical severe cancer pain scenario [6].

The World Health Organization (WHO) has provided recommendations for the pharmacological management of cancer pain in the form of a three-step "analgesic ladder," where the need for pain relief is met first by nonopioid analgesics, then weak opioids, and finally strong opioids [7]. However, these guidelines can be questioned with regard to the extent of efficacy as well as the rationale for only limited use of strong opioids. In recent years, many experts have suggested that the best approach to moderate-to-severe cancer pain is to tailor the dosage of the strong opioid as soon as possible and that opioid analgesics can be used at any stage of the disease, depending on the patient's condition [8]. Moreover, the quick progression of disease and the reduced life expectancy of patients with terminal cancer are reason enough to administer strong opioids [9]. This active treatment of cancer-related pain relative to the pain intensity of the patient can improve the satisfaction of the patients regarding the treatment; it also improves the quality of life (QOL) of the patients by relieving the fear of pain.

Furthermore, an essential aspect of cancer pain management that involves long-term analgesic therapy is the pharmaceutical technologies that ensure the controlled release of analgesic medications. The osmotic-controlled release oral delivery system (OROS) is an innovative drug delivery technology that uses osmotic pressure as the driving force to deliver pharmacotherapies; it is employed in many therapeutic areas [10]. OROS hydromorphone (Jurnista™, Janssen Pharmaceuticals, NV, Beerse, Belgium) is a novel, once-daily, long-acting, extended-release formulation of oral hydromorphone that serves to release hydromorphone in a continuous monophasic manner for up to 24 h [11–13]. Many previous studies have demonstrated the efficacy, safety, and tolerability of OROS hydromorphone in patients with chronic noncancer pain [11–13]. To date, although there have been several reports describing the efficacy of OROS hydromorphone in patients with cancer pain [14–17], the efficacy of OROS hydromorphone in patients with cancer pain whose pain had not been adequately controlled by other analgesics has not been evaluated.

Therefore, we evaluated the change in pain relief after OROS hydromorphone treatment in patients whose cancer pain had not been adequately controlled by other analgesics.

Patients and methods

This prospective, open-label, multicenter trial was conducted at 43 sites in South Korea. The study protocol was approved by the Institutional Review Board at each site, and the study was conducted in accordance with the Declaration of Helsinki.

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Patients

This study enrolled cancer patients ≥20 years of age whose cancer-related pain was deemed by the investigator to be inadequately controlled by other analgesics. Patients were excluded if they had a history of treatment with OROS hydromorphone or an allergy to hydromorphone, were unable to swallow solid oral formulations (for example, because of dysphagia, vomiting, paralytic ileus, or intestinal obstruction), or had taken monoamine oxidase inhibitors (such as moclobemide, selegiline, or toloxatone) within the 2-week period before study entry, because the concomitant use of central nervous system depressants with OROS hydromorphone may lead to respiratory depression, hypotension, and profound sedation [18]. All patients gave written informed consent before entering the study.

Study design

The primary objective of this study was to evaluate the clinical efficacy of strong opioid OROS hydromorphone for active pain control in patients suffering from cancer pain that had been inadequately controlled by other analgesics administered under the usual clinical circumstances. The secondary objective was to evaluate the following items in the OROS hydromorphone-treated patients: changes in QOL, Karnofsky performance status, degree of sleep disturbance, Patient's Global Assessment, Investigator's Global Assessment, and Clinical Global Impression-Improvement (CGI-I).

After the baseline evaluation (visit 1), OROS hydromorphone was administered. The second and third evaluations (visits 2 and 3) occurred 29±7 and 57±7 days later, respectively. To evaluate the clinical usefulness of the study drug, a strong opioid in the form of OROS hydromorphone was administered as a monotherapy between visits 1 and 2. Between visits 2 and 3, another strong opioid analgesic was permitted if the investigator deemed it necessary on the basis of the degree of pain control that had been achieved.

OROS hydromorphone was recommended to be administered once daily in the morning. Patients who had been previously treated with strong opioids underwent conversion to OROS hydromorphone, and then, the dose was titrated to obtain an individual dose. The initial dose in patient who currently received opioid analgesics was calculated on the basis of the daily dose of the previous narcotic agent using the standard equivalent pain ratio (AppendixS1). When required, all kinds of short-acting opioids were permitted as a rescue medication according to the decision of the investigators.

Assessments

The Numeric Rating Scale (NRS) and the percentage (%) of pain relief were used to evaluate pain intensity and the efficacy of the current pain treatment, respectively (AppendixS2). The primary efficacy measure was the pain intensity difference (PID) at visits 3 relative to visit 1, calculated as follows: % PID = [NRS (visit 1)−NRS (visit 3)] / NRS (visit 1) × 100. Sleep disturbance due to pain was assessed by recording the number of awakenings, the degree of sleep disturbance, and the sleep satisfaction (AppendixS3). The patients were asked to complete the Patient's Global Assessment (AppendixS4) and the Korean Functional Assessment Cancer Therapy-General (FACT-G) [19] (AppendixS5) questionnaires. In addition, the investigators completed the Karnofsky Performance Rating Scale (KPRS) (AppendixS6) and Investigator's Global Assessment (AppendixS7) questionnaires. They also completed a questionnaire asking about changes made to the OROS hydromorphone dose and the type of other analgesics that were used and why these changes were made (AppendixS8). The CGI-I questionnaire (AppendixS9) was also completed.

Statistical analyses

The sample size was determined on the basis of the difference in pain intensity between pre- and post-administration of the study drug (primary endpoint). For this, it was hypothesized that 50 % of the patients would show an improvement in pain intensity of more than 30 % after study drug administration. Given a sampling error with a 95 % confidence level of ±3 %, 1,051 patients were required. Considering that 20 % of the patients may withdraw from the study, the recommended sample size was 1,314 patients.

The patient data were mainly analyzed in three ways, namely intention-to-treat (ITT), full analysis set (FAS), and per-protocol (PP) analyses. The ITT analysis included the patients who were given at least one dose of the study drug. The FAS analysis included the patient population that remained after excluding patients who violated the major inclusion and exclusion criteria, who were never administered the study drug or who did not have efficacy data after drug administration. The PP analysis included the patients in the FAS analysis who completed the study according to the protocol. To analyze efficacy, both the FAS and PP populations were used.

The changes in pain intensity, FACT-G, KPRS, and sleep disturbance between visits 1 and 2 or between visits 1 and 3 were analyzed by using the Wilcoxon signed-rank test or paired t test. A P value of <0.05 was considered significant. All statistical analyses were performed by using SPSS for Windows software, version 15.0 (SPSS Inc., Chicago, IL).

Results

Study population

This clinical trial was conducted between February 1, 2009 and January 5, 2012. Figure 1 is a flow diagram showing patient

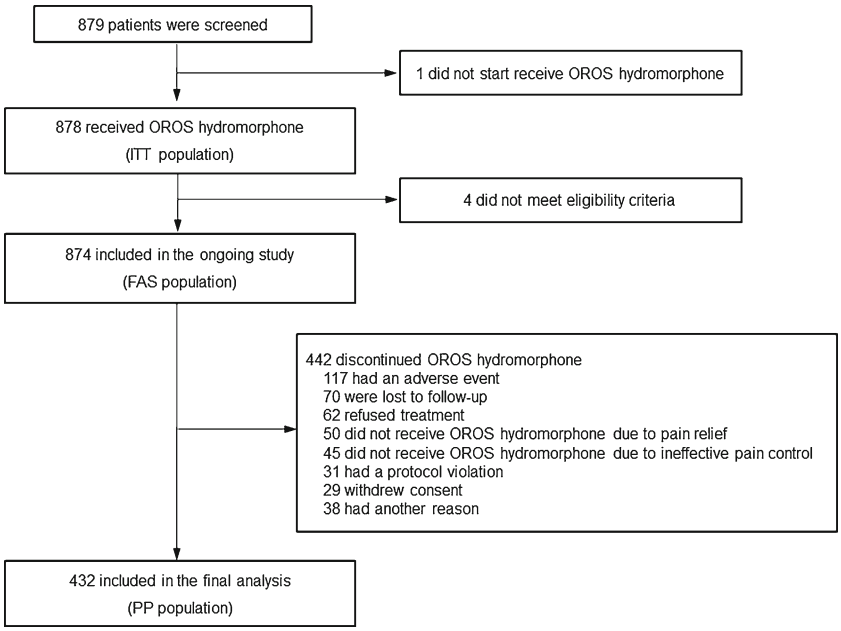

Fig. 1 Flow diagram of the patients who were enrolled in the study. *OROS* osmotic-controlled release oral delivery system, *ITT* intention to treat, *FAS* full analysis set, *PP* per protocol

entry and the reasons for premature discontinuation. Although a sample of 1,314 patients had been planned in this clinical trial, a total of 879 patients were screened due to a poor recruitment, among whom only one patient did not receive the study drug. Consequently, 878 patients received at least one dose of the study drug and were included in the ITT analysis. Since 4 of the 878 patients did not meet the eligibility criteria, 874 patients were included in the FAS analysis. At visits 2 and 3, 565 and 432 patients were evaluated, respectively. In total, 432 patients were included in the PP analysis: the 442 patients who discontinued the study drug prematurely were excluded. The most common reason for premature discontinuation was adverse events (n = 117, 26.5 %), followed by loss to follow-up (n = 70, 15.8 %), refusal of treatment (n = 62, 14.0 %), and no longer need for administration of the study drug for pain relief (n = 50, 11.3 %).

The baseline demographics and clinical characteristics of the patients included in the ITT analysis are shown in Table 1. The median age of the 878 patients was 63 years (range, 24–91 years). In total, 460 patients (52.4 %) had a good performance status (KPRS value ≥80 %). At the baseline evaluation, the mean NRS ± standard deviation (SD) of pain was 5.70±2.07, and 742 patients (84.5 %) reported moderate or severe pain. The most common analgesics used before study entry were strong opioids (502 patients, 57.2 %).

Extent of exposure to the study drug

The duration of exposure to OROS hydromorphone during the study (mean ± SD) was 40.1±22.1 days. Over the entire study duration, the daily dose (mean ± SD) was 16.6± 18.5 mg/day. Of the 565 patients who were evaluated at visit 2, 534 patients (94.5 %) continued taking OROS hydromorphone and 31 patients (5.5 %) stopped taking OROS hydromorphone. Of the latter patients, 9, 5, and 17 stopped taking the drug because of lack of pain relief, pain relief, and for other reasons, respectively.

Efficacy

Primary efficacy end point

Table 2 shows the changes in pain intensity at visits 2 and 3 relative to the initial assessment (visit 1). Of the 874 FAS patients, the PID in 343 patients (39.2 %) improved by more than 30 % at visit 3 relative to that at visit 1. Of the 432 PP patients, the PID in 282 patients (65.3 %) improved by more than 30 % at visit 3 relative to that at visit 1.

In the FAS population, the pain intensity (as indicated by mean NRS ± SD) at visits 1, 2, and 3 was 5.71±2.05, 4.54±2.41, and 4.26±2.58, respectively (Fig. 2a, P < 0.0001 for both visit 1–visit 2 and visit 1–visit 3). When the degree of pain relief was measured, the percentages of pain relief (mean ± SD) at visits 1, 2, and 3 were 44.8± 26.2, 56.0±26.1, and 58.6±27.1, respectively (Fig. 2b, P < 0.0001 for both visit 1–visit 2 and visit 1–visit 3). These effects of treatment on pain intensity and pain relief were also observed in the PP population.

Table 1 Demographic and baseline characteristics of the patients included in the intention-to-treat analysis

Characteristic	No. of patients (n=878)	
	No.	%
Age, years		
Median	63 (range, 24–91)	
Sex		
Male	537	61.2
Female	341	38.8
Karnofsky performance status		
KPRS value <50 %	96	10.9
50 % ≤ KPRS value < 80 %	322	36.7
KPRS value ≥ 80 %	460	52.4
Primary tumor site		
Lung	306	34.9
Stomach	113	12.9
Colorectal	80	9.1
Breast	61	6.9
Pancreas	46	5.2
Liver	26	3.0
Head and neck	24	2.7
Gallbladder	18	2.0
Esophagus	13	1.5
Others	191	21.8
Stage of disease (n=804)		
I	28	3.5
II	63	7.8
III	135	16.8
IV	578	71.9
Current anticancer treatment		
Yes	527	60.0
Chemotherapy	433	49.3
Radiotherapy	124	14.1
Others	28	3.2
No	351	40.0
Pain intensity (NRS) at visit 1		
Mean ± SD	5.70±2.07	
None	2	0.2
Mild (1–3)	134	15.3
Moderate (4–6)	422	48.1
Severe (7–10)	320	36.4
Previous used analgesics		
Nonopioid	155	17.7
Weak opioid	204	23.2
Strong opioid	502	57.2
Adjuvant analgesics	17	1.9

KPRS Karnofsky Performance Status Rating Scale, *NRS* Numeric Rating Scale, *SD* standard deviation

Secondary efficacy end points

Table 3 shows the secondary efficacy end point data. At visits 1, 2, and 3, total FACT-G scores (mean ± SD) were 52.01± 14.95, 52.38±15.14, and 52.75±15.18, respectively, but the differences in scores from visit 1 were not statistically significant (P=0.326 and P=0.055 for visit 1–visit 2 and visit 1–visit 3, respectively). At visits 1, 2, and 3, the KPRS values (mean ± SD) were 70.84±20.92, 70.45±20.58, and 70.01± 21.48, respectively (P=0.138 and P=0.044 for visit 1–visit 2 and visit 1–visit 3, respectively), which were maintained throughout the study period since the difference in the KPRS values between visits 1 and 3 was on average less than 1 point.

Assessment of the effect of treatment on sleep disturbances revealed that relative to the sleep disturbances recorded at visit 1, there were significant reductions in the degree of sleep disturbance and the number of awakenings at visits 2 and 3 (P<0.0001 for visit 1–visit 2 and visit 1–visit 3). The degree of sleep satisfaction also improved significantly (P<0.0001 for visit 1–visit 2 and visit 1–visit 3).

Of the 603 patients who participated in the Patient's Global Assessment, 364 patients (60.4 %) at visit 2 and 379 patients (62.9 %) at visit 3 said that the current pain management was effective. In addition, of the 603 investigators who participated in the Investigator's Global Assessment, 369 investigators (61.2 %) at visit 2 and 384 investigators (63.7 %) at visit 3 said that the current pain management was effective. Moreover, of the 603 investigators who participated in the CGI-I assessment, 340 investigators (56.4 %) at visit 2 and 362 investigators (60 %) at visit 3 said that the clinical status of his/her patients improved.

The changes in pain intensity according to baseline characteristics are shown in TableS1. The effect of pain relief was almost homogenous in all subgroups according to the Karnofsky performance status, primary tumor site, stage of disease, pain intensity at baseline, and type of previous used analgesics at visits 2 and 3. The exceptions were the patients with esophageal cancer (n=12, P=0.051) and the patients who previously received adjuvant analgesics (n=17, P= 0.063). These subgroups did not improve significantly, but the sample size of these two groups was too small to establish the statistical significance of this.

The changes in FACT-G according to baseline characteristics are shown in TableS2. Analysis of the changes in FACT-G between visits 1 and 3 according to baseline characteristics revealed that there was a significant improvement in QOL if the KPRS value was more than 50 % and less than 80 % (P= 0.0117), if the primary tumor was breast cancer (P=0.0361), if the disease was in stage III (P=0.0041), if pain intensity at baseline was severe (P=0.0012), or if the previously used analgesics were nonopioids (P<0.0001). If the primary tumor

Table 2 Changes in the numeric rating scales at visits 2 and 3 relative to visit 1

	Total number	% PID ≥ 30					
		Visit 2			Visit 3		
		n	%	95 % CI	*n*	%	95 % CI
FAS population	874	302	34.6	31.4–37.7	343	39.2	36.0–42.5
PP population	432	237	54.9	50.2–59.6	282	65.3	60.8–69.8

PID pain intensity difference, *FAS* full analysis set, *PP* per protocol, *CI* confidence interval

was liver cancer, there was a statistically significant reduction in QOL ($P=0.049$).

Discussion

The objective of this study was to evaluate the efficacy of active pain control with strong opioid OROS hydromorphone in patients whose cancer pain was inadequately controlled by other analgesics. The present study showed that OROS hydromorphone was beneficial in the cancer pain management of patients who have sustained pain with other analgesics in PP population although the FAS population did not satisfy the hypothesis of this study.

Strong opioids should be considered as a very important instrument in the "ethical" care of all patients with cancer pain. There is no evidence that a specific strong opioid is superior to another and that an agent that works for a particular patient is the "right" drug. However, continuous-release opioid formulations are advocated for the management of chronic cancer pain because they can provide more consistent, around-the-clock pain relief with a decreased dosing frequency [20]. OROS hydromorphone may be particularly well suited to the long-term management of cancer pain because it provides

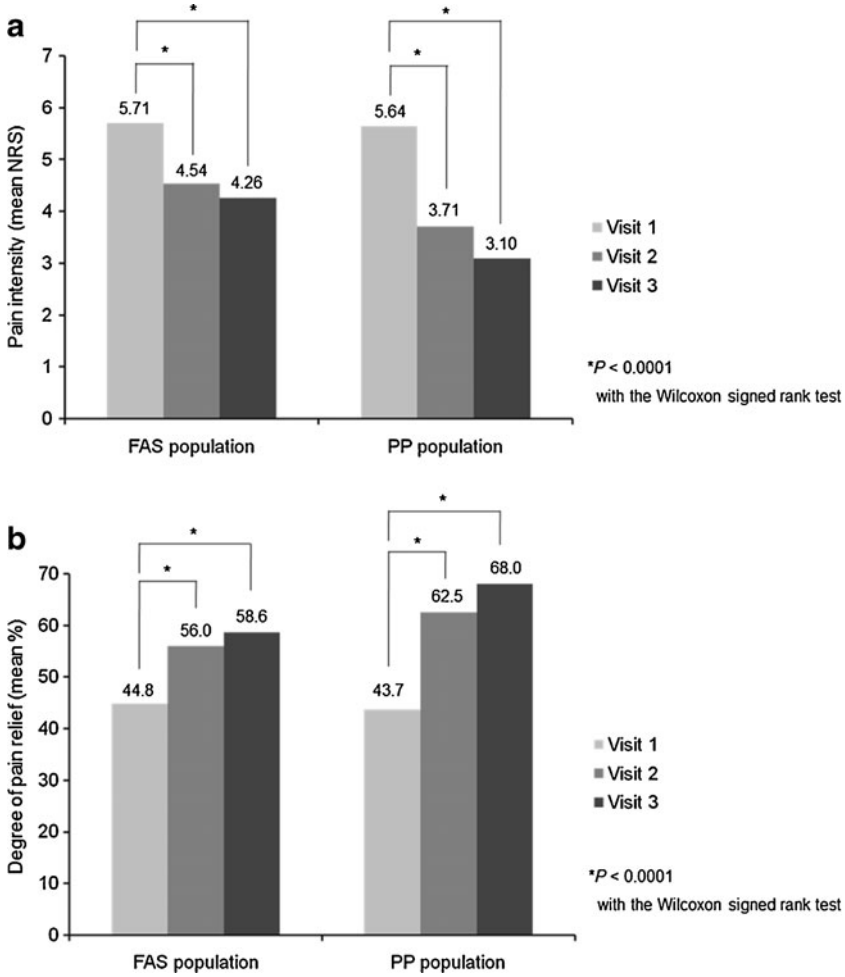

Fig. 2 Changes in pain intensity as determined by **a** the numeric rating scale and **b** the percentage of pain relief. *NRS* numeric rating scale, *FAS* full analysis set, *PP* per protocol

Table 3 Secondary end point results

Secondary end points	Visit 1		Visit 2		*P* value (visit 1–visit 2)	Visit 3[a]	*P* value (visit 1–visit 3)
	n	Mean ± SD	*n*	Mean ± SD		Mean ± SD	
Korean FACT-G, mean ± SD							
Physical subscale	815	11.34±5.34	811	11.91±5.49	<0.0001[b]	12.05±5.55	<0.0001[b]
Social subscale	815	13.54±4.75	811	13.73±4.58	0.1523[c]	13.69±4.62	0.1912[c]
Emotional subscale	811	15.05±5.18	807	14.93±5.14	0.4319[c]	15.15±5.09	0.2129[c]
Functional subscale	811	12.09±5.81	807	11.81±5.74	0.0843[c]	11.86±5.84	0.1131[c]
Total	811	52.01±14.95	807	52.38±15.14	0.3262[c]	52.75±15.18	0.0552[c]
Karnofsky performance status (%)	874		874				
KPRS		70.84±20.92		70.45±20.58	0.1384[b]	70.01±21.48	0.0438[b]
Sleep disturbance	874		874				
NRS		4.38±3.18		3.35±2.93	<0.0001[c]	3.22±3.02	<0.0001[c]
Number of awakenings		1.88±1.75		1.46±1.64	<0.0001[c]	1.36±1.66	<0.0001[c]
Number of patients (%)							
None		295 (33.8)		217 (50.2)		269 (62.3)	
Once and twice		278 (31.8)		165 (38.2)		116 (26.9)	
More than three		301 (34.4)		50 (11.6)		47 (10.9)	
Level of sleep satisfaction		5.26±2.84		6.05±2.77	<0.0001[c]	6.25±2.86	<0.0001[c]
Patient's Global Assessment			603				
Effective, number of patients (%)				364 (60.4)		379 (62.9)	
Investigator Global Assessment			603				
Effective, number of investigators (%)				369 (61.2)		384 (63.7)	
CGI-I			603				
Improvement, *n* (%)				340 (56.4)		362 (60.0)	

FACT-G Functional Assessment Cancer Therapy-General, *SD* standard deviation, *KPRS* Karnofsky Performance Status Rating Scale, *NRS* Numeric Rating Scale, *CGI-I* Clinical Global Impression-Improvement

[a] Last observation carried forward

[b] Paired *t* test

[c] Wilcoxon signed-rank test

consistent plasma concentrations, sustained analgesia, and convenient once-daily dosing [21]. Previous short- and long-term studies demonstrate the efficacy, safety, and tolerability of OROS hydromorphone using a variety of dosing strategies. However, most studies were carried out in patients with chronic noncancer pain, and only four studies have been performed in patients with cancer pain [14–17]. The results of these studies, along with those of the present study, are summarized in Table 4. Hanna et al. compared the efficacy and safety of once-daily OROS hydromorphone with that of a twice-daily sustained release formulation of morphine in patients with chronic cancer pain. OROS hydromorphone provided consistent pain relief over a 24-h period, and the pain levels in the evening were significantly lower after OROS hydromorphone treatment than after treatment with the sustained release formulation of morphine [14]. The results of a 1-year extension of the above study suggest that long-term repeated dosing with once-daily OROS hydromorphone can be beneficial for the continual management of persistent, moderate-to-severe cancer pain [15]. Two studies evaluated the efficacy and safety of conversion to once-daily OROS hydromorphone from previous opioid analgesics in patients with chronic cancer pain. Wallace et al. reported that patients with chronic cancer pain can easily convert from a previous opioid therapy to a maintenance dose of OROS hydromorphone [16]. Lee et al. evaluated the effectiveness and safety of OROS hydromorphone in reducing breakthrough pain when it was used to replace a previous opioid analgesic [17]. Once-daily OROS hydromorphone was efficient in reducing cancer pain-related breakthrough pain episodes and medications, including end-of-dose pain, probably due to its longer duration of action. In the present study, we evaluated the efficacy of OROS hydromorphone in patients with cancer pain that had been inadequately controlled by other analgesics applied under the usual clinical circumstances. Compared to previous studies of OROS hydromorphone for cancer pain relief, the present results showed for the first time that OROS hydromorphone provided

Table 4 Studies of OROS hydromorphone in patients with cancer pain

Study number	Objective	Study design	Study and control drugs	Number of patients	Duration of dosing	Comments
Controlled studies						
DO-118 (Hanna et al. [14])	To demonstrate clinical equivalence of OROS HM ER with IR HM and morphine (IR and SR) using "worst pain in the past 24 hours" item of Brief Pain Inventory	Multicenter, randomized, double-blind, parallel-group study	HM IR and OROS HM ER IR and SR morphine	200	Titration 2–9 days Maintenance 10–15 days	Comparison of OROS HM ER and SR morphine
Uncontrolled studies						
DO-118X (Hanna et al. [15])	To characterize pain control achieved with long-term repeated dosing of OROS HM ER	Multicenter, open-label, single-treatment, repeated dose, 1-year extension study	OROS HM ER once daily	68	Mean duration of exposure 139 days	Efficacy of OROS HM ER in the long-term management
DO-104 (Wallace et al. [16])	To assess the efficacy and tolerability of conversion to OROS HM ER from previous strong opioids	Multicenter, open-label, single-treatment, repeated dose study	OROS HM ER once daily	127	Prior opioid stabilization ≥3 days Titration 3–21 days Maintenance 14 days	Conversion from standard opioid therapy to OROS HM ER Efficacy and safety of conversion
HYD-KOR-4001 (Lee et al. [17])	To evaluate the effectiveness of OROS HM ER in reducing breakthrough pain medication frequency	Multicenter, open-label, single-treatment study	OROS HM ER once daily	114	Titration 2–9 days Prior opioid stabilization 3 days Observation 7 days Titration 7 days	Conversion from standard opioid therapy to OROS HM ER Reduction of breakthrough pain
HYD-KOR-5009	To evaluate whether OROS HM ER provided pain relief in patients with pain inadequately controlled by other analgesics	Multicenter, open-label, single-treatment study	OROS HM ER once daily	874	Titration 4 weeks Maintenance 4 weeks	Efficacy of OROS HM ER in treating pain inadequately controlled by other analgesics

OROS osmotic-controlled release oral delivery system, *HM* hydromorphone, *ER* extended release, *IR* intermediate release, *SR* sustained release

effective pain relief in a comparatively large number of cancer patients, whose pain had been inadequately controlled by other analgesics. It is thought that the reason why OROS hydromorphone proved to be effective in this group of cancer patients was that it provided consistent pain relief over a 24-h period and decreased breakthrough pain including end-of-dose pain via its long duration of action, as was observed in the previous four studies.

This pain relief was achieved consistently regardless of the performance status, the primary tumor site, the stage of disease, the pain intensity at baseline, and the type of previously used analgesics during the study period. Moreover, OROS hydromorphone not only effectively relieved the cancer pain in patients whose pain had not been controlled previously by nonopioids or weak opioids but also significantly improved the cancer pain of patients who converted from a previous strong opioid therapy to OROS hydromorphone: the mean NRS of the patients who were treated previously with strong opioids dropped from 5.70±2.02 to 4.59±2.35 after administering OROS hydromorphone (TableS1, $P<0.0001$). Notably, the mean NRS of these patients decreased not only when the dose of OROS hydromorphone was increased (the NRS dropped from 6.09±1.96 to 4.81±2.31, $P<0.0001$) but it also fell when the dosage of OROS hydromorphone was maintained (from 5.48±2.05 to 4.52±2.35, $P<0.0001$) or reduced (from 5.78±1.65 to 3.93±2.48, $P<0.0001$) (data not shown). This is significant because opioid rotation is regularly used with patients who fail on a certain opioid; the rotation either involves changing the opioid drug or changing the route of administration [22]. Oldenmenger et al. reported that in patients with advanced cancer whose cancer-related pain is unstable and refractory to other opioids, continuous parenteral hydromorphone often results in long-lasting adequate pain control and should be considered even after extensive pretreatment with opioids [23]. Therefore, conversion from previous strong opioid therapy to OROS hydromorphone can be achieved without loss of pain control.

Although OROS hydromorphone treatment was effective in providing pain relief, it did not improve patient QOL. It might be difficult to improve the QOL via pain management because most patients in the present study had advanced or metastatic cancer and were undergoing cytotoxic treatments. In the case of patients with breast cancer, which has a relatively good prognosis, QOL improved. However, in the case of patients with liver cancer, which has a relatively poor prognosis, QOL decreased because of the rapid progression of liver cancer.

There are several limitations that should be considered in interpreting the results of the present study. First, although a sample of 1,314 patients had been planned in this clinical trial, only 878 patients (66.8 %) were registered due to a poor recruitment. Moreover, FAS population did not satisfy the hypothesis of this study that the PID in more than 50 % of the patients would improve by more than 30 %, although this hypothesis was satisfied in the PP population. Second, a large number of patients ($n=442$, 50.6 %) did not complete the study because the study period was relatively long (8 weeks) compared to that of other studies, which examined the short-term efficacy of opioids (1–2 weeks). However, this is not unexpected given the severity and progressive nature of the disease; in fact, a large number of patients did not complete the study due to study drug-unrelated reasons. Dropouts due to lack of efficacy ($n=45$, 5.1 %) or adverse drug reaction ($n=40$, 4.6 %) were uncommon. Third, this was a single-arm and open-label study, so the results cannot be compared directly to those of other opioid therapies.

In conclusion, this study suggested that OROS hydromorphone is beneficial in the pain management in cancer patients whose cancer-related pain was inadequately controlled by other analgesics that were used under usual clinical circumstances. Therefore, it is recommended that the strong opioid OROS hydromorphone be used for the active management of cancer pain that cannot be relieved by other analgesics.

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Conflict of interest We declare that no conflict of interest exists for any of the authors.

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