ORIGINAL ARTICLE

Oral Prolonged-Release Oxycodone-Naloxone: Analgesic Response, Safety Profile, and Factors Influencing the Response in Patients With Advanced Cancer

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■ **Abstract**

Background: Oxycodone-naloxone (OXN) aims to reduce opioid-related constipation while being successfully analgesic.

Methods: We evaluated the analgesic response, prevalence, and severity of side effects in 176 patients with cancer who had moderate to severe pain and were being treated with OXN. Patients were followed for 28 days and evaluated every 7 days. Pain intensity, changes of therapy, and adverse drug reactions were recorded at each visit. The primary efficacy endpoint was the proportion of responders (≥30% reduction of pain intensity from baseline to final) and final average pain score ≤ 4 on a scale of 0 to 10.

Results: Average and worst pain intensity and breakthrough pain (BTP) prevalence decreased over time, and 81.3% of patients were responders. The starting daily dose of OXN was raised from 25.1 ± 13.0 mg to 44.1 ± 29.9 mg, and dose escalation > 5%/day was observed in 19.4% of patients; 40.8% to 46.2% and 11.0% to 17.0% experienced any constipation and a severe grade of constipation during the follow-up visit, respectively. Digestive system tumor, thyroid endocrinopathies, psychological irritability, and BTP increased the risk for analgesic nonresponse.

Conclusions: OXN had a strong analgesic effect in patients with moderate to severe cancer pain; the safety profile is in line with the common adverse effects of opioids, and severe constipation was uncommon.

Clinical Trial Registration: NCT02293785. ■

Key Words: oxycodone-naloxone, patients with cancer, analgesia, constipation, factors influencing the response

BACKGROUND

Pain is a widespread problem that affects 39.3% to 66.4% patients with cancer, depending on the stage of the disease and ongoing treatments.[1] The preferred therapy is mainly pharmacological, as suggested by the guidelines and recommendations of several scientific societies.[2–4] When pain intensity is moderate to severe (>5 out of 10 points measured on the numeric rating scale [NRS]), opioids are the suggested analgesic of choice. However, opioids sometimes have limitations, mainly the lack or the loss of an effective analgesic response and/or severe and unmanageable adverse drug reactions (ADRs). In the first case, nonresponders (NRs) are the patients whose pain intensity does not decrease by at least 30% from the basal score[5]; conversely, responders (Rs) are the patients who achieve a reduction in pain intensity of 30% or more. In the second case, the opioid-induced toxicity is so high that continuing the treatment becomes unacceptable for the patients. ADRs often include drowsiness, confusion, nausea, constipation, and dry mouth. These ADRs frequently persist, affecting patients and requiring symptomatic interventions to reduce their negative impact. Constipation in particular occurs frequently and may be due to the cancer itself, especially in the advanced phases of the disease. In addition, reduced physical activity, food intake, hydration, and sometimes digestive system cancers increase the risk for bowel dysfunction, with hard dry stools, incomplete evacuation, bloating, abdominal cramping, constipation, and increased gastric reflux.[6] Introducing opioids worsens gastroenteric impairment because of their pharmacological action. By binding their gastroenteric receptors, they reduce gastric emptying and stimulate pyloric tone, resulting in nausea and vomiting.[7] They also inhibit intestinal propulsion, increasing fluid absorption and the amplitude of nonpropulsive segmental contractions. These effects result in a reduced ability to evacuate the bowel, abdominal cramps, and pain.[8,9] Tolerance to μ opioid agonists occurs in all gastrointestinal organs except the colon.[10,11] This is why constipation persists while the other gastrointestinal symptoms improve with long-term opioid treatment.

To overcome this problem, a fixed combination of oral prolonged-release oxycodone-naloxone (OXN) in a 2:1 ratio was developed, mitigating the opioid-induced constipation. The efficacy of the combination is based on binding of the μ-agonist oxycodone to intestinal opioid receptors, which is strongly opposed by the opioid receptor antagonist naloxone, due to its higher affinity. At the same time, the bioavailability of oral naloxone is poor (<3%) due to extensive hepatic first-pass metabolism. This pharmacokinetic mechanism stops naloxone from interfering with the central analgesic action of oxycodone.

Observational studies have assessed the efficacy and tolerability of OXN in cancer pain,[12–15] showing that it

attained the same analgesic response as other opioids but with better control of constipation. It is therefore worth bearing in mind that differences in the response of patients to analgesic drugs can lead to treatment failure or to ADRs even among patients given the same dose of the same drug. A drug's activity depends on the interaction of the drug itself with molecules involved in absorption, distribution, metabolism, and elimination. In addition, an increasing amount of data indicate that single nucleotide polymorphism of some genes, albeit not directly involved in modulation of the levels of the proteins for which they are encoding, seem to alter the activity of the protein and may have an important role in defining responding and nonresponding patients.

The evaluation of the analgesic response to OXN in patients with cancer who have moderate to severe pain was the primary objective of the study, obtained by measuring the difference of worst, average, and least pain intensity experienced in the preceding 24 hours before and after the treatment, and by calculating the percentage of responders (Rs) and nonresponders (NRs). Possible reasons of the analgesic variability were detected, correlating the response with some clinical and genetic factors. Single nucleotide polymorphisms, in genes coding for the proteins involved in the response to OXN, were tested to evaluate potential influence on the analgesic response. The safety profile during the OXN therapy, with special attention to the presence and severity of constipation, was a secondary objective of the study. Additionally, we aimed to investigate changes in treatment schedules of OXN over time.

METHODS

Study Design and Patients

This was an Italian, multicenter, prospective, observational study including patients with cancer who had moderate to severe pain requiring WHO step III opioids and who were being treated with OXN (NCT02293785). Each center involved in the study obtained the approval of its institutional review board. All patients gave written informed consent before any study-related activities. Eligibility criteria included evidence of locally advanced or metastatic tumor; persistent moderate to severe cancer pain, with average pain intensity (API) ≥ 4 experienced in the preceding 24 hours; need for background treatment with WHO step III strong opioids never previously administered, practicable with OXN; and age > 18 years and life expectancy > 1 month, based on clinical estimates. Exclusion criteria concerned patients with cerebral tumors or leukemia due to different pain mechanisms; patients receiving concurrent analgesic radiotherapy or first-line ongoing chemotherapy, or nonpharmacological analgesic treatments; pre-existing chronic renal failure; or psychiatric diseases limiting mental competence and judgment.

After the baseline visit, follow-up lasted for 4 weeks, and follow-up visits were scheduled on days 7, 14, 21, and 28. This was an observational study carried out in the clinical practice. In this frame, physicians usually adopt different therapeutic choices along with the same indication. Once the physicians freely chose to administer OXN based on their clinical experience and knowledge, it was proposed to the patient to enter the study. According to clinical practice, they were also free to plan the whole therapy schedule over the follow-up period, including the use of other analgesic drugs such as WHO step I drugs administered concomitantly with WHO step III drugs.

Endpoints

The efficacy endpoints included the evaluation of 3 levels of pain intensity: API, worst pain intensity (WPI), and least pain intensity (LPI), all referring to the 24 hours before every visit. The pain intensity difference (PID), referring to API between the initial and final visits, was considered the starting point to evaluate the analgesic response.

The PID enabled us to classify patients as either NRs or Rs. To define the Rs, we applied the following double criterion: the achievement of at least 30% pain reduction and a final pain intensity score of ≤ 4 points. Both criteria have already been described as methods to distinguish analgesic response in chronic cancer and noncancer pain.[5,16] The combined use of these 2 criteria has already been proposed[17] and applied in a previous study.[18] Patients who did not meet both these criteria were considered as NRs.

Daily dose changes were established during the observation period. The level of satisfaction with the analgesic therapy received was checked at all visits. The frequency of BTP before and after OXN treatment was recorded.

Secondary efficacy endpoints were the number of switches to another opioid because of inadequate analgesia and the need for supplementary opioids or adjuvant analgesic drugs to optimize pain control.

Safety was checked at each visit by recording the ADRs,[19] defined as any unpleasant reaction occurring or worsening in intensity and/or frequency that developed after the administration of the first dose of the treatment (ie, OXN) and thus attributable to the treatment itself.

We investigated the associations between the primary tumor site, concomitant diseases, psychological profile, type of pain, and analgesic response to OXN to assess potential relationships between the analgesic response and clinical variables. Similarly, we examined whether polymorphisms of some candidate genes, known to be potential influencing factors,[20–22] were related to the condition of NR in our sample.

Measures

Pain intensity (API, WPI, LPI) in the 24 hours prior to the visit was measured on an NRS ranging from 0 (no pain) to 10 (the worst pain imaginable). Patients were considered NRs when they did not achieve a ≥30% reduction in API[5] and/or did not achieve a final NRS pain score of ≤4.[16] Patients who met both these criteria were classified as Rs.

The presence of neuropathic pain was evaluated using the Douleur Neuropathique 4 (DN4) questionnaire.[23]

A score of >4 allowed us to classify pain as neuropathic. Conversely, pain was classified as nociceptive. Clinicians were asked to evaluate whether pain was exclusively neuropathic or mixed (ie, neuropathic and nociceptive), based on their experience. BTP was detected according to the Davies algorithm.[24]

OXN daily dose was determined at each visit, and the number of patients requiring a mean increase in the daily dose of >5%, according to the Opioid Escalation Index (OEI),[25] was recorded.

The level of satisfaction with the analgesic therapy was assessed using a 6-point verbal rating scale (from "certainly satisfied" to "certainly dissatisfied"). Performance status was measured with the Karnofsky Performance Status (KPS) Scale; psychological aspects (anxiety, worry, irritability, and depression) were investigated using 4 items extracted from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30) version 3.[26]

ADRs were assessed with the Therapy Impact Questionnaire,[27] a self-reported scale investigating the presence and severity of symptoms using a 4-point verbal rating scale (ie, no, little, moderate, severe). Only ADRs reported at least once as moderate or severe (hereinafter called severe ADRs) and with a frequency higher than 10% in the whole sample were included in the toxicity analyses.

Genetic Measures and Analysis. Genomic DNA was extracted from blood samples with a Maxwell 16 DNA Purification Kit (Promega, Italia Srl, Milan, Italy). Three OPRK1 polymorphisms (rs7815824, rs702764, and rs1051660), 1 OPRM1 polymorphism (rs1799971), 1 CYP3A5 polymorphism (rs776746), 2 CYP2D6 polymorphisms (rs16947, rs3892097), and 1 intergenic polymorphism (rs9353027) were genotyped with TaqMan SNP Genotyping assays (Thermo Fisher Scientific, Milan, Italy). Polymerase chain reaction (PCR) was performed in 384-well plates, prepared with the automatic liquid handling system epMotion 5075 (Eppendorf, Milan, Italy). The PCR-amplified DNA fragments were analyzed with allelic discrimination sequence detection software (Thermo Fisher Scientific).

Patients with the above-mentioned characteristics were included in the analysis to assess the role of demographic characteristics, pain and other clinical features, comorbidities, and administered treatments in influencing the occurrence of severe ADRs.

Baseline Evaluations

At baseline, the main demographic characteristics, educational level, oncological medical history (primary tumor site, local or metastatic progression, previous and ongoing cancer treatments), concomitant morbidities, KPS score, and psychological aspects were recorded. Assessment of pain included duration, type of pain (nociceptive, neuropathic, or mixed), BTP, pain intensity (API, WPI, LPI), pain therapy, and level of satisfaction with the therapy.

Follow-up

At each visit, API, WPI, LPI, and BTP were evaluated. Changes of analgesic therapy (daily dose, type[s], and dose[s] of extra opioids or adjuvant drugs), opioid switches or discontinuations, and ADRs were recorded.

Final Visit

The final visit could be either at the end of follow-up (day 28) or at the time of the switch, or at early discontinuation of the study for any reason.

At the last available visit, all the parameters evaluated at the previous visits, KPS score, psychological aspects,

and satisfaction with the analgesic therapy received were collected.

Statistical Analysis

Assuming a proportion of NRs to OXN of 30% and at least a 15% prevalence of polymorphism, 174 patients were to be included to detect an odds ratio > 3 with 80% power and 5% type 1 error for a bilateral test. Expecting a proportion of drop-outs of 15%, 200 patients had to be enrolled. Participants who provided informed consent, had no major violations of the eligibility criteria, had received at least 1 OXN dose, and had at least 1 response evaluation were included in the analysis (Analysis set II [AS-II]).

Safety and secondary efficacy analysis were done on AS-II. The primary efficacy analysis was run on patients from AS-II who had an available genetic analysis (Analysis set I [AS-I]).

Each patient was monitored until the end of the 28-day follow-up, or until a drug switch or premature discontinuation of the study for any reason. In case of premature discontinuation of the opioid, the last observation-carried-forward method was applied to handle missing data only in the graphic representation of pain intensity over time.

Patients' characteristics were summarized using absolute and relative frequencies for categorical variables; means, standard deviations (SDs), and medians a were used for continuous variables.

Associations between clinical variables and polymorphisms on response were analyzed with logistic regression models adjusted for baseline API. In view of the small number of the genotypes with a double mutant allele, a dominant genotypic model was used to analyze the polymorphism effect on response. The primary and secondary endpoints were obtained as the absolute and relative frequencies, with 95% confidence intervals (CIs) calculated by exact binomial methods.

For safety analysis, the incidence rates of toxicities were compared between the baseline visit (without OXN) and the second visit (with OXN) by running the nonparametric McNemar's test.

RESULTS

Thirteen Italian centers—7 palliative care services and 6 oncology wards—were involved in the study and contributed in the enrollment of 206 patients between November 2014 and February 2016. The exclusion of 4 patients due to major violations and of 11 due to nonevaluable responses resulted in an AS-II population of 191 patients. In the AS-II analysis set, 176 patients also received an evaluable genetic analysis and were included in the AS-I population (Figure 1).

The main patient characteristics at baseline, including demographic data, educational level, history of tumor, KPS score, concomitant diseases, psychological aspects, and synthetic schedule of therapy, are set out in Table 1.

Table 2 describes the pain at baseline, including duration, type, background therapy on the basis of World Health Organization guidelines, adjuvant analgesic treatments, intensity (API, WPI, and LPI), and BTP.

In all, 137 out of 176 patients (75.4%) continued OXN treatment up to the 28th day of follow-up. In the

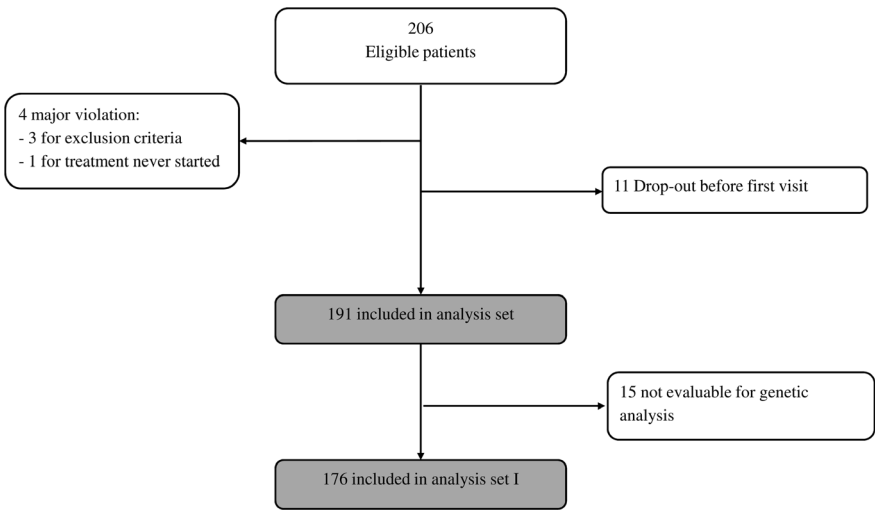

Figure 1. GREAT Study flow-chart.

Table 1. Main Demographic and Clinical Characteristics of the Patients at Baseline—Analysis Set I

Demographic and clinical characteristics at baseline (Analysis Set I)	OXN 176 patients
Age, mean years (SD)	68.5 (10.0)
Female, *n* (%)	78 (44.3)
Education, *n* (%)	
Illiterate	2 (1.1)
Elementary	55 (31.3)
Lower middle	46 (26.1)
Higher middle	59 (33.5)
Degree	14 (8.0)
Primary site of tumor, *n* (%)	
Respiratory system	65 (36.9)
Digestive system	48 (27.3)
Urinary-reproductive system	31 (17.6)
Other/unknown site	13 (7.4)
Head/neck	10 (5.7)
Breast	9 (5.1)
Presence and sites of metastasis, *n* (%)	145 (82.4)
Lymph node	60 (41.4)
Bone	57 (39.3)
Lung	40 (27.6)
Abdominal	19 (13.1)
Brain	15 (10.3)
Tumors with local progression, *n* (%)	70 (39.8)
Years from first primary tumor diagnosis, mean (SD)	2.3 (4.0)
Concomitant diseases, *n* (%)	123 (69.9)
Hypertension	74 (42.0)
Diabetes	39 (22.2)
Heart diseases	16 (9.1)
Thyroid endocrinopathy	14 (8.0)
Chronic obstructive pulmonary disease	13 (7.4)
Prostatic hypertrophy	9 (5.1)
Rheumatic diseases	8 (4.5)
Gastropathies	7 (4.0)
Mixed anxiety-depressive disorder	4 (2.3)
Chronic liver disease	3 (1.7)
Kidney failure	3 (1.7)
Psychological aspects and quality of life the 7 days before visit 1	
Stress (any degree), *n* (%)	136 (77.3)
Worry (any degree), *n* (%)	154 (87.5)
Irritability (any degree), *n* (%)	106 (60.2)
Depression (any degree), *n* (%)	139 (79.0)
Perceived health, mean score (SD)	3.4 (1.3)
Perceived quality of life, mean score (SD)	3.4 (1.3)
Previous antineoplastic therapies, *n* (%)	128 (72.7)
Baseline antineoplastic therapies, *n* (%)	50 (28.4)
Baseline concomitant therapies, *n* (%)	129 (73.3)
Baseline therapies for symptoms other than pain, *n* (%)	70 (39.8)

SD, standard deviation; OXN, oxycodone-naloxone.

39 patients who discontinued, 53.8% completed at least 3 cycles of OXN treatment (14 days). The main reasons for interruption were the change of opioid (n = 17, 43.6%), transfer to another care center (n = 8, 20.5%), loss to follow-up (n = 7, 17.9%), and other reasons (n = 7, 17.9%).

The efficacy outcomes are reported in Table 3. The primary efficacy outcome of Rs, evaluated by the double criterion, was 143 out of 176 (81.3%; 95% CI: 74.7 to 86.7). Satisfaction with treatment showed changes in

Table 2. Assessment of Pain at Baseline—Analysis Set I

	Overall 176 patients
Pain duration, mean months (SD)	3.4 (3.8)
Type of pain, *n* (%)	
Only nociceptive	142 (80.7)
Both nociceptive and neuropathic	34 (19.3)
Only nociceptive, type of pain related to localization	
Visceral, *n* (%)	101 (71.1)
Bone, *n* (%)	39 (27.5)
Soft tissue, *n* (%)	31 (21.8)
Background pain therapy, *n* (%)	
No therapy (WHO step 0)	22 (12.5)
Therapy WHO step I	71 (40.3)
Therapy WHO step II	83 (47.2)
Adjuvant therapies for pain, *n* (%)	82 (46.6)
Steroids	56 (68.3)
Anticonvulsants	14 (17.1)
Antidepressants	14 (17.1)
Bisphosphonates	9 (11.0)
Other	8 (9.8)
Average pain intensity, mean score (SD)	6.2 (1.1)
Worst pain intensity, mean score (SD)	8.3 (1.4)
Least pain intensity, mean score (SD)	4.0 (2.1)
Breakthrough pain, *n* (%)	80 (45.5)

SD, standard deviation.

Table 3. Efficacy Outcomes—Analysis Set I and Analysis Set II

Analysis Set I (176 patients)	Baseline	Last Visit*
Average pain intensity (API), mean score (SD)	6.2 (1.1)	2.9 (1.8)
Worst pain intensity (WPI), mean score (SD)	8.3 (1.4)	4.6 (2.4)
Least pain intensity (LPI), mean score (SD)	4.0 (2.1)	1.6 (1.7)
Primary efficacy endpoint, *n* (%)		
Responder (R)		143 (81.3)
Nonresponder (NR)		33 (18.7)
Reasons for nonresponse, *n* (%)		
PID < 30%		5 (15.2)
Final API > 4		3 (9.1)
PID < 30% and final API > 4		25 (75.8)
Breakthrough pain, *n* (%)	80 (45.5)	63 (35.8)
Level of satisfaction with therapy, *n* (%)		
Certainly satisfied	2 (1.1)	35 (19.9)
Very satisfied	1 (0.6)	47 (26.7)
Quite satisfied	12 (6.8)	61 (34.7)
Neither satisfied nor dissatisfied	20 (11.4)	14 (8.0)
Quite dissatisfied	85 (48.3)	17 (9.7)
Certainly dissatisfied	56 (31.8)	2 (1.1)
OXN daily dose, mean mg (SD)	25.1 (13.0)	44.1 (29.9)

Analysis Set II (191 patients) Secondary Efficacy Endpoints	*n*	% (95% CI)
OEI > 5%	37	19.4 (14.0 to 25.7)
Switch because of inadequate analgesia	10	5.2 (2.54 to 9.42)
Patients requiring additional opioids	53	27.7 (21.5 to 34.7)
Patients requiring adjuvant drugs	159	83.2 (77.2 to 88.2)

*For each patient, the last visit with OXN. CI, confidence interval; *N*, total number of subjects; OEI, opioid escalation index; OXN, oxycodone-naloxone; PID, pain intensity different; SD, standard deviation.

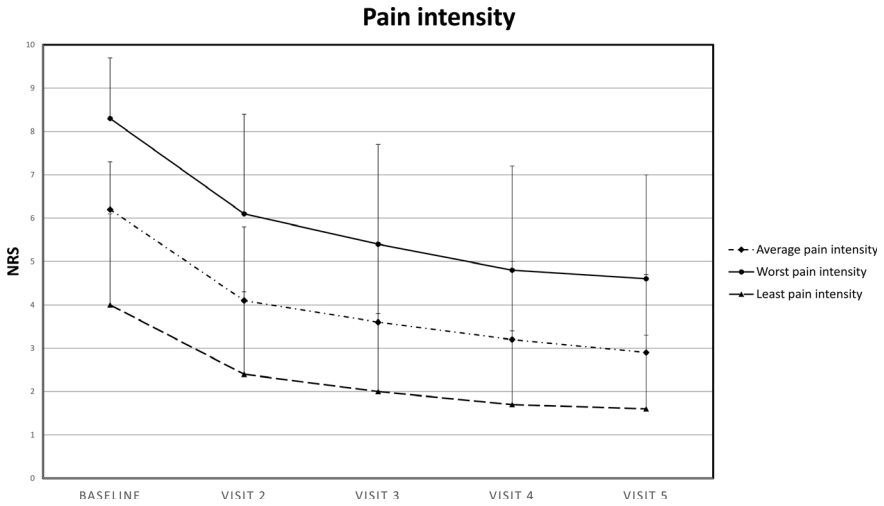

Figure 2. Pain intensity over time. NRS, numeric rating scale.

positive satisfaction from 8.5% before OXN to 81.3% at the end of the observation. The mean OXN daily dose was increased about 75% during the follow-up (28 days), and OEI > 5% was observed in 19.4% of the patients (95% CI: 14.0 to 25.7). Switches to deal with inadequate analgesia were made in 5.2% of the cases (95% CI: 2.54 to 9.42); 27.7% of patients required additional opioids at the last visit.

The pain intensity time curves are illustrated in Figure 2: API, WPI, and LPI decreased over time, showing the effectiveness of OXN in the management of chronic cancer pain.

The statistically significant results of primary efficacy analysis are reported in Table 3 and the complete results are available online (Table S1).

No polymorphism had any significant effect on response to OXN (Table S2, online materials). The statistically significant covariates on response adjusted for the baseline mean pain were "primary tumour in digestive system" ($P = 0.050$), "thyroid endocrinopathy" ($P = 0.023$), "psychological irritability" ($P = 0.023$), and BTP ($P = 0.035$) (Table 4).

A detailed description of the type and severity of the ADRs recorded in patients treated with OXN is reported in Table 5, and the maximum observed toxicity is described in Table S3.

A statistically significant increase in the percentage of any degree of toxicities between the first and second visits (ie, after starting OXN treatment) was recorded for drowsiness, confusion, nausea, and dry mouth.

There was no statistically significant increment in the incidence of severe toxicities, and the rate of severe gastralgia decreased during OXN treatment. The prevalence and severity of constipation did not show any significant change during the observation period.

Table 4. Concomitant Clinical Conditions Influencing the Analgesic Response

Number of patients	NRs 33 *n* (%)	Rs 143 *n* (%)	*P* value	OR (95% CI)
Tumor digestive system—Yes	14 (42.4)	34 (23.8)	0.050*	0.43 (0.18 to 1.00)
Concomitant diseases				
Thyroid endocrinopathy—Yes	6 (18.2)	8 (5.6)	0.023*	0.26 (0.08 to 0.83)
Psychological aspects—Irritability				
No	8 (24.2)	62 (43.4)	0.029*	Reference
Little	12 (36.4)	54 (37.8)		0.50 (0.18 to 1.34)
A lot or extremely	13 (39.4)	27 (18.9)		0.25 (0.09 to 0.69)
Baseline BTP—Yes	20 (60.6)	60 (42.0)	0.035*	0.42 (0.19 to 0.94)

BTP, breakthrough pain; CI, confidence interval; NRs, nonresponders; OR, odds ratio; Rs, responders.
*indicates significance of *P* value < 0.050

DISCUSSION

The analgesic efficacy of OXN administered to patients with cancer was on average high. The API, WPI, and LPI scores were essentially halved from baseline to final visit. In particular, during treatment, the API score decreased to 2.9 (±1.8 SD), with a substantial reduction of 50% to 60%. Such a reduction widely exceeds the Farrar criterion,[5] which defines a 30% reduction as a clinically relevant outcome. It also agrees with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations[28] indicating a pain reduction of ≥50% as substantially improved pain

Table 5. Frequency of Patients With ADRs in OXN—Analysis Set II

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Baseline vs. Visit 2
Number of patients[‡]	191	191	169	159	147	*P* value[†]
Drowsiness						
Any degree	45 (23.6)	81 (42.4)	72 (42.6)	70 (44.0)	61 (41.5)	<0.001*
Severe	9 (4.7)	15 (7.9)	21 (12.4)	19 (11.9)	15 (10.2)	0.109
Confusion						
Any degree	25 (13.1)	38 (19.9)	36 (21.3)	37 (23.3)	34 (23.1)	0.024*
Severe	3 (1.6)	4 (2.1)	8 (4.7)	9 (5.7)	8 (5.4)	0.705
Nausea						
Any degree	32 (16.8)	45 (23.6)	36 (21.3)	34 (21.4)	29 (19.7)	0.024*
Severe	5 (2.6)	7 (3.7)	6 (3.6)	10 (6.3)	6 (4.1)	0.527
Vomiting						
Any degree	10 (5.2)	14 (7.3)	11 (6.5)	10 (6.3)	11 (7.5)	0.317
Severe	1 (0.5)	4 (2.1)	3 (1.8)	5 (3.1)	3 (2.0)	0.180
Constipation						
Any degree	74 (38.7)	87 (45.5)	78 (46.2)	69 (43.4)	60 (40.8)	0.080
Severe	29 (15.2)	21 (11.0)	25 (14.8)	27 (17.0)	21 (14.3)	0.182
Dry mouth						
Any degree	42 (22.0)	62 (32.5)	51 (30.2)	54 (34.0)	49 (33.3)	<0.001*
Severe	13 (6.8)	15 (7.9)	11 (6.5)	14 (8.8)	9 (6.1)	0.617
Hallucinations						
Any degree	2 (1.0)	7 (3.7)	8 (4.7)	8 (5.0)	7 (4.8)	0.059
Severe	—	—	2 (1.2)	—	—	—
Muscle spasm/myoclonus						
Any degree	17 (8.9)	15 (7.9)	13 (7.7)	10 (6.3)	12 (8.2)	0.593
Severe	2 (1.0)	1 (0.5)	2 (1.2)	1 (0.6)	1 (0.7)	0.564
Gastralgia						
Any degree	27 (14.1)	29 (15.2)	14 (8.3)	15 (9.4)	14 (9.5)	0.724
Severe	11 (5.8)	3 (1.6)	2 (1.2)	2 (1.3)	2 (1.4)	0.011*
Dysuria						
Any degree	9 (4.7)	10 (5.2)	9 (5.3)	6 (3.8)	8 (5.4)	0.739
Severe	1 (0.5)	1 (0.5)	3 (1.8)	2 (1.3)	1 (0.7)	—
Breathlessness						
Any degree	14 (7.3)	14 (7.3)	14 (8.3)	13 (8.2)	9 (6.1)	1.000
Severe	—	1 (0.5)	2 (1.2)	1 (0.6)	1 (0.7)	—
Itching						
Any degree	10 (5.2)	10 (5.2)	12 (7.1)	10 (6.3)	7 (4.8)	1.000
Severe	1 (0.5)	1 (0.5)	1 (0.6)	1 (0.6)	1 (0.7)	1.000

*$P < 0.05$. [†]*P* value: McNemar's test. [‡]We displayed the total number of study participants at baseline while we reported only the number of participants who took OXN during the last week for the following visits ADRs, adverse drug reactions; OXN, oxycodone-naloxone.

control. Variability in the responses was observed: 143 patients (81.3%) were classified as Rs, based on the double criterion applied, and 33 (18.7%) did not achieve a pain reduction of ≥30% and a final score of ≤4 points. The achieved pain reduction and the percentage of Rs suggest an overall good analgesic result, consistent with patients' satisfaction. Satisfaction with analgesic care is not the same as the pain intensity score indicated by the patients. Satisfaction represents a more qualitative evaluation, and in this study, it was evaluated by means of a 6-point verbal rating scale ranging from certainly satisfied to certainly unsatisfied. Before OXN treatment was administered, 8.5% of patients gave positive evaluations (ie, certainly, very, and quite satisfied). By the end of the follow-up period, 81.3% of the sample felt satisfied about the treatment. In addition, the percentage of patients with BTP at baseline was 45.5% and dropped to 35.8% at the final visit, suggesting better background pain control and success in managing most of the breakthrough episodes. A previous study[29] indicated that the response to opioids and the patients' pain intensity could be influenced by several clinical factors, such as pain features, comorbidities, and ongoing therapy. Herein, we found that a primary tumor site in the digestive system, a psychological profile characterized by severe irritability, and BTP were clinical factors strongly increasing the likelihood of a negative response to OXN. In particular, the role of BTP was consistent with a previous study in which 723 patients with cancer who had BTP showed unsatisfactory pain relief compared to patients who did not have BTP episodes.[30] Conversely, with regard to the effects of clinical variables on the analgesic response, the finding that thyroid endocrinopathy positively influenced the analgesia was surprising,

and we did not find clinical references about this evidence. However, we found an experimental study[31] showing an important increase in μ-opioid receptors and an upregulation of encephalin and dynorphin activities in many brain areas of hypothyroid adult rats. Herein, we were not able to demonstrate that genetic polymorphisms induced variables in analgesic responses. Only polymorphism rs3892097 - TT+CT trended toward but did not reach a significant difference between Rs and NRs. This lack of clear evidence probably reflects the small sample size of patients.

Analyzing the safety profile, any degree of drowsiness, confusion, nausea, and dry mouth tended to increase after starting OXN, and their prevalence remained unvaried during follow-up. Conversely to our expectations, we did not find a descrease in these symptoms presence and severity over time, as the supposed onset of tolerance to these ADRs did not begin at all. Constipation was under particular surveillance, given that it usually worsens during opioids treatment,[32] but it might also improve. Due to OXN administration, in this study, the degree of constipation did not change, either in prevalence or in severity, indicating that the μ-opioid agonist and antagonist, administered orally together, maintained a correct balance in regulating bowel motility.

Among the secondary efficacy endpoints, we considered changes in the daily dose of OXN over time, which increased from the initial 25.1 mg to the final 44.1 mg (referring to oxycodone). These were low dosages, corresponding to about 38 to 66 mg/day of equivalent oral morphine. Low-dose escalation in 4 weeks could be considered as an indicator of limited tendency to develop tolerance. A balance between analgesic efficacy and low and stable drug dosages is generally a sign of positive treatment. Comparing some secondary efficacy endpoints between this study and another study where oxycodone was administered alone,[33] the opioid escalation index was >5% in 19.4% of OXN patients and 19.2% with Oxycodone (OXY), while participants requiring switches for pain-related reasons were 5.2% with OXN and 12% with OXY. Finally, we should acknowledge a limitation of the present study. Given the observational nature of the study, it is not possible to compare the efficacy and safety of OXN to other treatments. This study reflects the real medical practice in which the physician evaluates patients' needs and plans the treatment. This last reason leads us to prefer an observational study to a controlled one. Further studies should be aimed at controlling these variables to obtain a more detailed description of OXN administration and its consequences.

CONCLUSION

This study confirms that OXN achieves a good analgesic response in patients with cancer who have moderate to severe pain. Moreover, it does not influence constipation and it guarantees a good safety profile. The analgesic effect was supported by oxycodone, which is the agonist opioid contained in OXN. The pain reduction observed in this study was compliant with the analgesia normally observed with oxycodone[33] and confirmed the evidence of other studies on OXN. Constipation remained unchanged during follow-up, supporting a positive influence of OXN on bowel function. In addition, the results provide important information about the proportion of patients achieving good or inadequate overall responses to this analgesic therapy, suggesting the need to investigate the causes of noneffectiveness and potential strategies to overcome it.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Effects of clinical variables on response corrected by baseline mean pain.

Table S2. Effects of polymorphism variables on response corrected by baseline mean pain – Analysis Set I.

Table S3. Proportion of patients who presented ADRs during OXN follow-up.

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APPENDIX

Good Response with Appropriate Treatment (GREAT) Collaborators

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