

Use of oxycodone controlled-release immediately after NSAIDs: a new approach to obtain good pain control

L. TESSARO¹, E. BANDIERI², G. COSTA³, G. FORNASIER⁴, V. IORNO⁵,
C. PIZZA⁶, G. PASTACALDI⁷, G. MICHELETTO⁸

¹Pain and Palliative Care, Unità Locale Socio Sanitaria (ULSS) 8, Asolo (Italy)

²Unit of Oncology, Carpi e Mirandola Hospital, Modena, Italy

³Pain Therapy Department, Camposampiero Hospital, Camposampiero (Padova) (Italy)

⁴Unit of Pain Therapy and Palliative Care, Belluno (Italy)

⁵Pain Therapy Department, Policlinico Mangiagalli Regina Elena, Milan (Italy)

⁶Oncology Unit, ASLNA4, San Giuseppe Vesuviano (Italy)

⁷Palliative Care and Pain Therapy Unit, Dolce e Misericordia Hospital, Prato (Italy)

⁸Unit of Palliative Care, Unità Locale Socio Sanitaria (ULSS) 13, Mirano (Italy)

Abstract. – Introduction: Opioids are recommended as appropriate therapy for the treatment of cancer pain and chronic non-malignant pain. Oxycodone is an alternative agent to its parent compound, morphine, and is available in a controlled-release (CR) formulation that allows convenient twice-daily dosing. The aim of this study was to evaluate the efficacy and tolerability of oxycodone CR as first-line therapy in patients with chronic cancer or non-cancer pain that was not relieved by non-steroidal anti-inflammatory drugs (NSAIDs).

Methods: This was a prospective, open-label, multicentre trial carried out in 8 pain and oncology centres in Italy. Patients (n=309) with NSAID-refractory chronic cancer (55.7%), non-cancer (39.4%) or mixed (4.9%) pain (rating of 4-10 on a numerical rating scale [NRS] from 0-10) were enrolled. Patients were treated with oral oxycodone CR twice daily for at least 28 days. Dosage was individualized for each patient and up-titrated over the first week of treatment. The primary endpoint was reduction in NRS score for pain. Secondary endpoints were tolerability, quality of life and patient assessment of treatment efficacy.

Results: A significant decrease (57%) in pain intensity was recorded during the first week of therapy (decrease in NRS score from 7.85 ± 1.4 to 3.35 ± 1.8 ; $p < 0.00001$). Overall, there was a 72.3% reduction in NRS pain score from baseline at the end of the study. Quality of life significantly ($p < 0.005$) improved during oxycodone therapy, and 91% of patients rated treatment as “effective” or “very effective”. Five patients stopped oxycodone CR treatment because of adverse events, and one stopped treatment because of dysphagia.

Conclusions: The results of this study demonstrate the efficacy and tolerability of oxycodone CR in patients with moderate-to-severe pain of a variety of aetiologies and confirm the feasibility and effectiveness of moving directly from step I to step III on the WHO analgesic treatment ladder.

Key Words:

Oxycodone controlled release (CR), NSAID-refractory pain, Chronic pain, Cancer pain, Analgesia.

Introduction

Advanced cancer is associated with moderate-to-severe pain in up to half of all patients, and up to three-quarters of European patients with cancer reported that they also experienced pain^{1,2}. Guidelines recommend the addition of an opioid when relief of cancer pain is inadequate during treatment with non-opioid analgesics such as paracetamol [acetaminophen] and/or non-steroidal anti-inflammatory drugs (NSAIDs)³⁻⁵. Stepwise escalation of analgesic treatment for the management of cancer pain is advocated in the World Health Organization (WHO) Guidelines, with therapy initially consisting of non-opioid analgesics (\pm adjuvant) for mild pain (step [or ladder] I), followed by a mild opioid (\pm non-opioids \pm adjuvant) for mild-to-moderate pain (step [or ladder] II) and finally a strong opioid (\pm non-

opioids \pm adjuvant) for moderate-to-severe pain (step [or ladder] III)⁴.

Non-cancer-related pain is also a significant healthcare issue, affecting up to one-third of the population in developed countries⁶. The causes of chronic non-cancer pain are diverse and include musculoskeletal, neurological and trauma, amongst others, making its management challenging. Opioids are approved by the American Academy of Pain Medicine and the American Pain Society for the treatment of chronic non-malignant pain, both overall⁷ and in older patients⁸.

The use of opioids in cancer pain and palliative care, and in the acute treatment of moderate-to-severe acute non-cancer pain, is widely accepted⁹. The working party included specialists in cancer pain and in non-cancer pain as we were aiming at focusing on pain and its causes and features, irrespective of the type of patient (i.e. patients with and without malignancy).

Oxycodone is a semi-synthetic agent and is an alternative to its parent compound, morphine, for providing opioid analgesic therapy. Data from a meta-analysis indicate that the efficacy and tolerability of oxycodone in patients with cancer pain are similar to those of morphine¹⁰ and oxycodone has also demonstrated greater efficacy than morphine in visceral pain^{11,12}. Although there have been no studies comparing oxycodone with morphine in neuropathic pain, in such patients, oxycodone CR has been shown to be effective both in enhancing existing gabapentin therapy¹³ and, in a comparison study of combination therapy with pregabalin versus pregabalin alone¹⁴, combination therapy produced greater alleviation of neuropathic pain and greater improvements in quality of life than monotherapy. Combination therapy also allowed a dose reduction of both agents and had a superior safety profile compared with monotherapy¹⁴.

Oxycodone is available in a controlled-release (CR) preparation, which enables a twice-daily dosing frequency¹⁵. CR preparations of both oxycodone and morphine are recognised as appropriate for use in step II or III therapy by the European Society of Medical Oncology (ESMO).

This study investigated the efficacy and safety of therapy with oxycodone CR, started immediately after NSAID therapy, in patients with chronic cancer or non-cancer pain that was not relieved by NSAIDs. As far as the Authors are aware, this is the first study to use oxycodone as first choice after NSAIDs. In a previous study of

22 cancer patients treated with oxycodone CR, patients did not take opioids in the 2 weeks prior to enrolment, but it was not specified whether they had ever taken opioids¹⁶.

Patients and Methods

Patients

Patients had chronic pain that was not relieved by treatment with NSAIDs. Eligibility criteria were as follows: (i) age ≥ 18 years; (ii) moderate-to-severe cancer or non-cancer pain (rating of 4-10 on a numerical rating scale [NRS] from 0-10) with indication for opioid treatment according to WHO ladder guidelines; (iii) no previous or ongoing treatment with opioids. Patients were excluded from the trial based on the following criteria: (i) severe renal dysfunction (creatinine >3 mg/dL), (ii) moderate-to severe hepatic dysfunction; (iii) poor cognitive function, or diagnosed psychiatric or mental illness; (iv) a history of drug abuse; (v) inability to take oral medications; (vi) cerebral metastases; (vii) pregnancy or breastfeeding. All patients provided written informed consent to participate in the study.

Study Design

The study was designed as an open-label, prospective, multicentre trial carried out at 8 oncology and pain therapy centres in Italy from June to December 2008. The trial was co-ordinated by one of the Authors of this paper (LT) Unità Locale Socio-Sanitaria (ULSS8) Asolo site, and was approved by the Local Ethic Committees. The study was conducted according to Declaration of Helsinki guidelines (revised 2005 version).

Treatment

Patients received oral oxycodone CR (Oxy-Contin® [Mundipharma Italia]) for at least 28 days. The drug was administered twice daily according to the manufacturers prescribing information. The starting dose of oxycodone CR was determined on an individual basis for each patient, depending on the indication for pain relief, then dosages were adjusted to maintain adequate pain relief (defined as an NRS score of ≤ 3). The initial mean dosage of oxycodone CR was 11.36 ± 9.58 mg/day. Due to the risk of side effects with long-term therapy, NSAID treatment was interrupted as the principal form of analgesia.

Measurements

Pain intensity was assessed at study entry (baseline) and during 6 follow-up visits; the first 3 follow-up visits occurred during the first 7 days of oxycodone CR therapy (on days 1, 3 and 7) and were part of dosage titration, then the remaining 3 visits took place at 1-week intervals. Patients were asked to rate pain during the past 24 hours on an NRS scale from 0 = no pain to 10 = worst pain imaginable. The primary efficacy endpoint was reduction from baseline in NRS score for pain. A 2-point reduction has been described as being clinically meaningful^{17,18}. To evaluate the tolerability of treatment, adverse events (AEs) were recorded at each follow-up visit.

Secondary endpoints were evaluation of the impact of pain on quality of life (QoL) and patient assessment of treatment efficacy. The Brief Pain Inventory (BPI) questionnaire, completed at baseline and at each follow-up visit, was used to evaluate the impact of pain on everyday life during the treatment^{19,20}. The BPI questionnaire evaluates pain intensity on a NRS (0 = no pain to 10 = worst pain imaginable) and the impact of pain on QoL by rating pain interference across seven domains (general activity, mood, walking ability, work, sleep, relation with other people, life enjoyment) on a numerical scale (0 = does not interfere to 10 = completely interferes). At each follow-up visit patients were also asked to rate the effectiveness of treatment as not effective, slightly effective, effective or very effective.

Statistical Analysis

Data were tested statistically according to the Student's *t*-test and chi-squared test. Statistical significance was defined as $p < 0.05$.

Results

Patients

Over a 6-month period, 360 patients were evaluated and 309 with NSAID-resistant moderate-to-severe chronic pain (rating of 4-10 on a NRS scale from 0-10) were included in the study. Baseline characteristics for the patient population are provided in Table I.

Of the 309 patients treated with oxycodone CR, 297 patients (96.11%) remained on therapy

Table I. Patients characteristics.

Characteristic	Patients population (n = 309)
Patients who completed the study (n)	297
Age (years) [median \pm SD (range)]	67.1 \pm 12.61 (31-94)
Sex [n (%)]	
Men	154 (51.9)
Women	143 (48.1)
Aetiology of pain (% patients)	
Cancer	55.7
Non cancer	39.4
Mixed	4.9
Type of pain (% patients)	
Somatic	24.3
Neuropathic	14.1
Visceral	8.2
Mixed	53.4

for the full study period (28 days) and 12 patients discontinued the treatment. Of these, 3 were lost at follow-up, 3 died, 5 stopped taking oxycodone CR treatment because of AEs and 1 stopped the treatment because of dysphagia (Figure 1).

Pain Control

The percentage of patients reporting low NRS scores (0-3) increased markedly during treatment with oxycodone CR (Figure 2). Pain intensity, as assessed by the NRS, decreased consistently throughout the 28-day treatment period: the mean NRS score decreased from 7.84 at baseline to 2.17 at study end (Figure 3). A statistically significant decrease ($p < 0.00001$) in pain intensity (57%) was achieved within the first week of treatment with oxycodone CR; the NRS score decreased from 7.84 at baseline to 3.35 after 1 week of therapy (Figure 3). In fact, the improvement in NRS score for pain was statistically significant compared with baseline from the first day of therapy ($p < 0.00001$) (Figure 3). At the end of the study, treatment with oxycodone CR had resulted in a 72.3% reduction in NRS pain score compared with baseline.

Upwards titration of the oxycodone CR dosage was required to control pain, with the mean starting dosage of oxycodone CR (11.36 ± 9.58 mg/day) adjusted to 21.21 ± 19 and 25.91 ± 21.49 mg/day after 7 and 28 days, respectively (Figure 3).

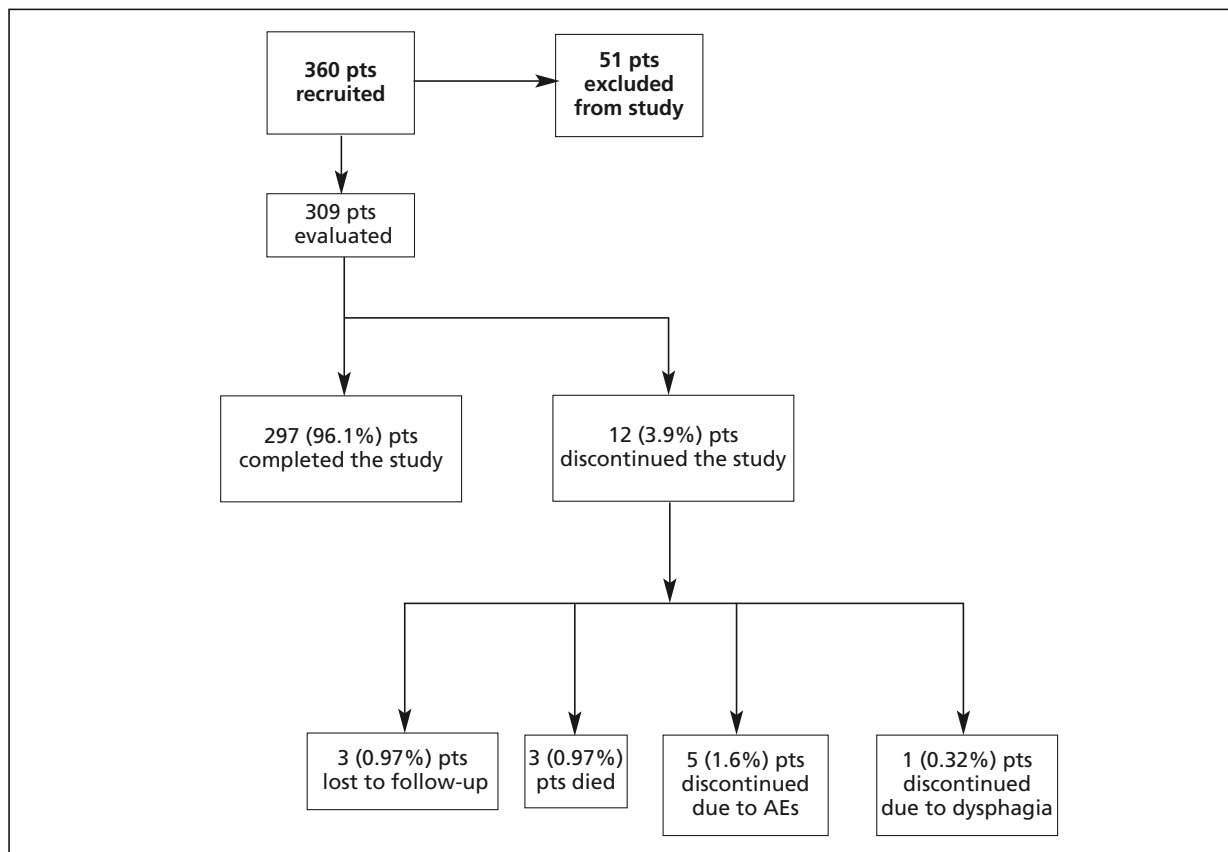


Figure 1. Flow of patients through the study. AEs = adverse events; pts = patients.

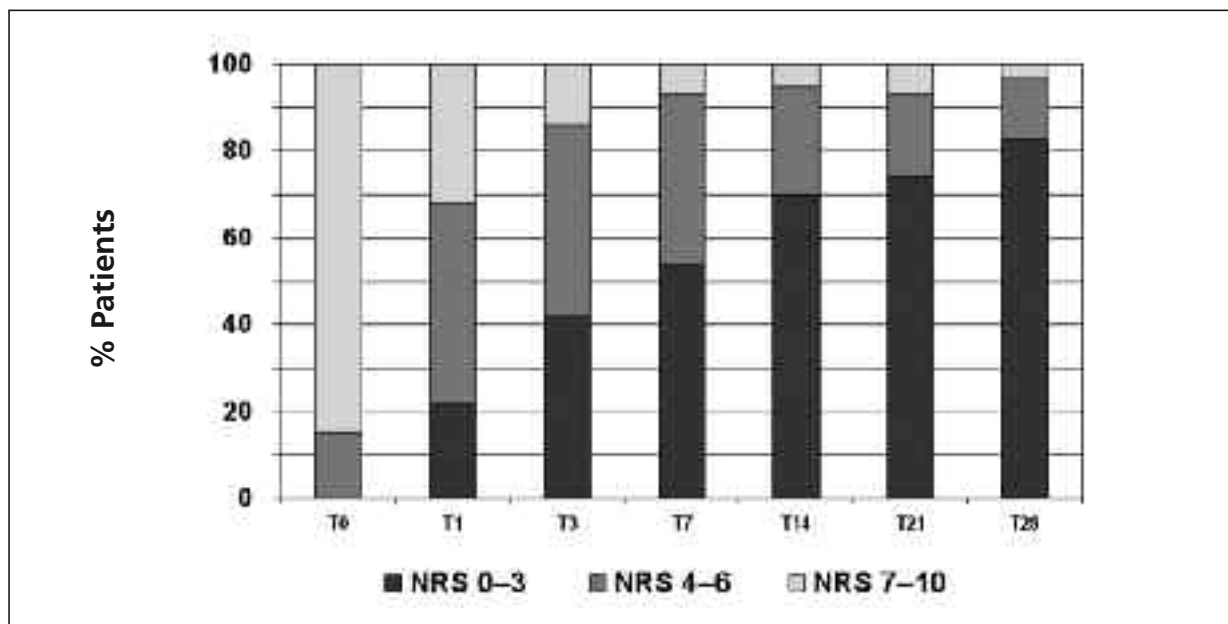


Figure 2. Percentage of patients with different numerical rating scale (NRS) scores over time.

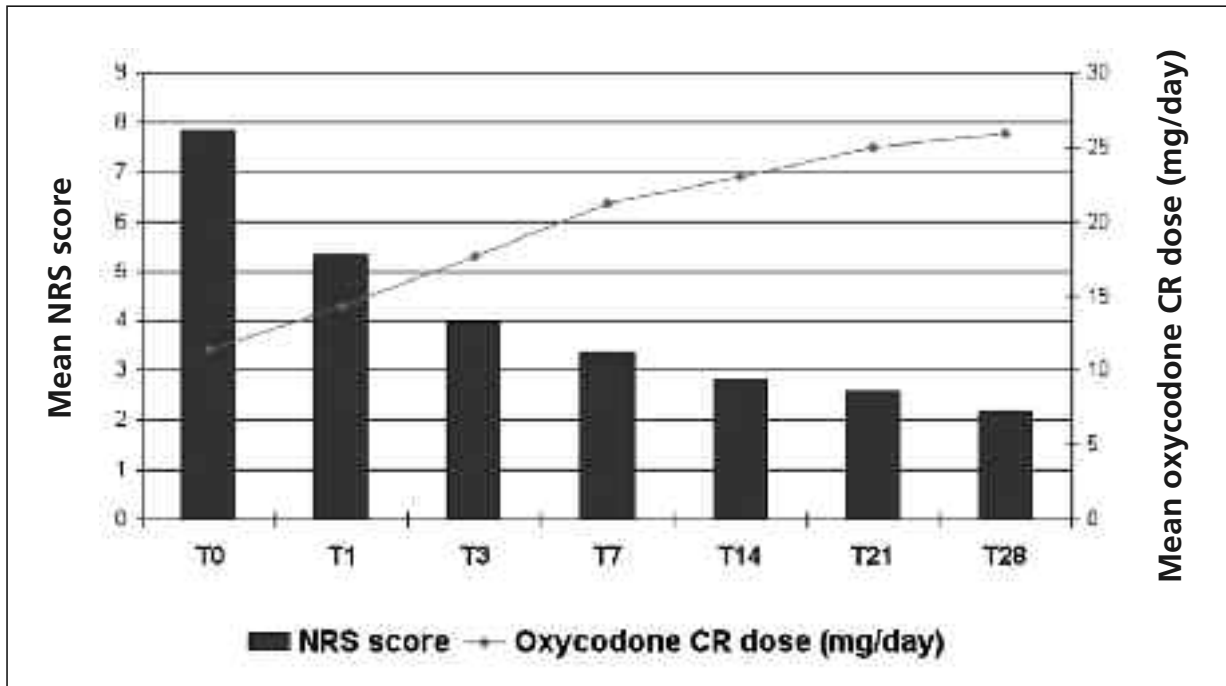


Figure 3. Mean numerical rating scale (NRS) score for pain and mean oxycodone controlled-release (CR) dose in patients with chronic pain.

Quality of Life

QoL improved statistically significantly ($p < 0.005$) during oxycodone CR therapy (Figure 4). Consistent improvements were documented across all domains of the BPI.

Patient Satisfaction

At the end of the study, oxycodone CR therapy was rated as “effective” or “very effective” by 91.0% of patients (Figure 5).

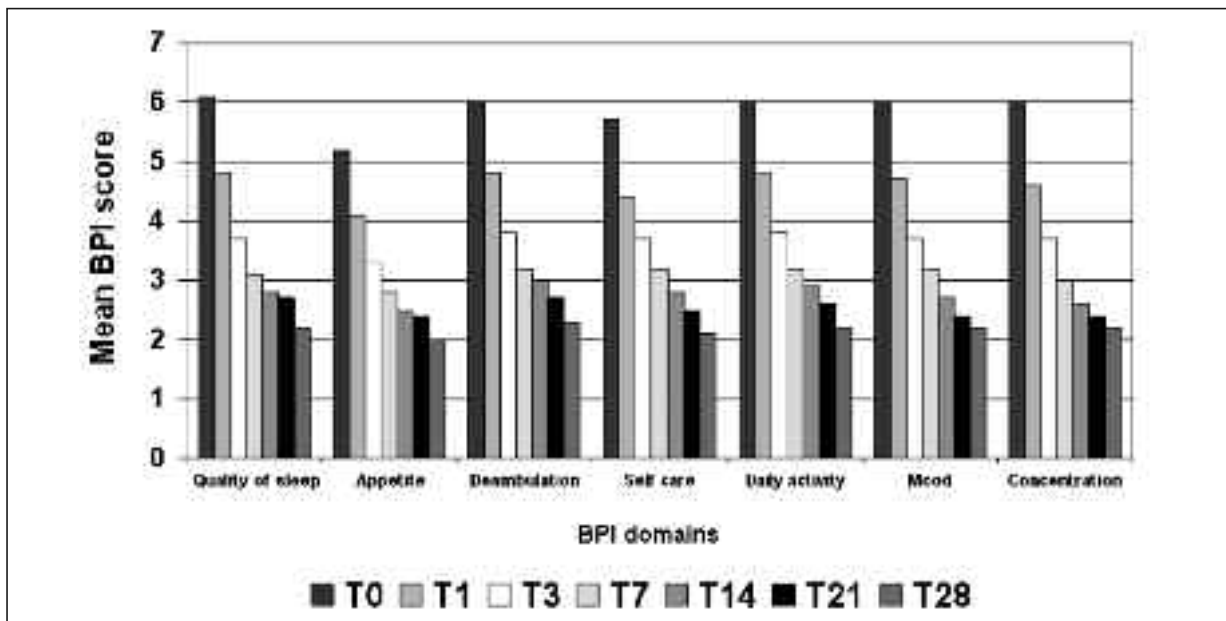


Figure 4. Influence of pain on quality of life scores. BPI = Brief Pain Inventory.

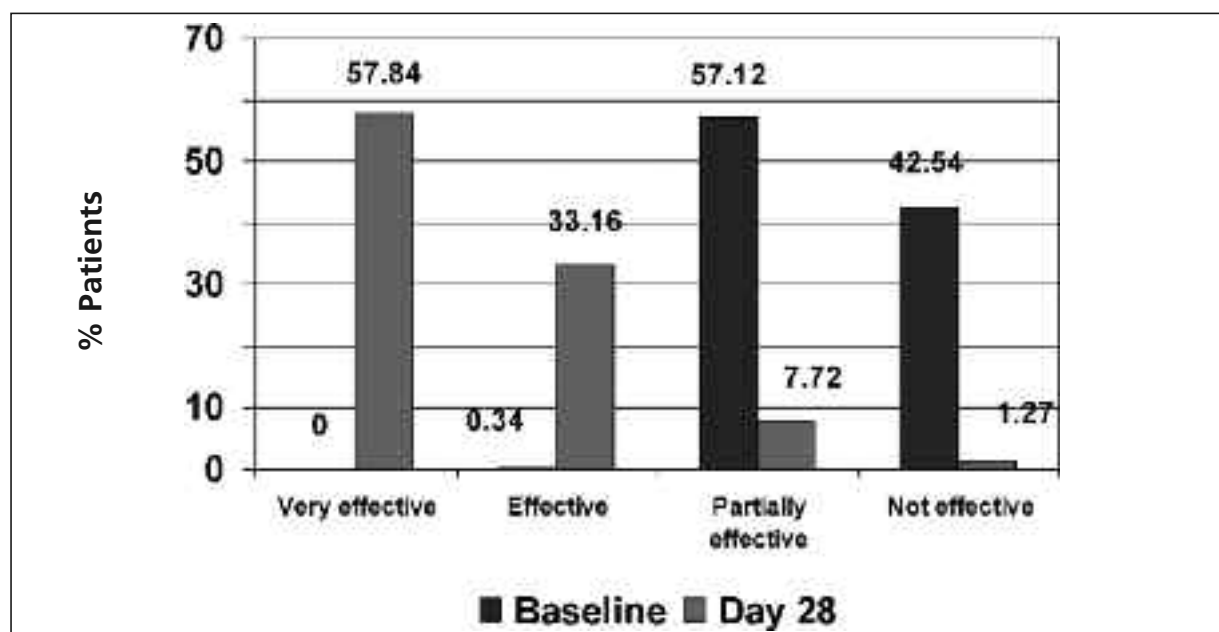


Figure 5. Patient satisfaction with pain relief therapy at baseline and at the end of treatment with oxycodone controlled-release (CR) (28 days).

Tolerability

Oxycodone CR was well tolerated. No side effects were reported in approximately 50% of patients, weak side effects in approximately 40%, moderate side effects in approximately 10% and heavy side effects in 0.7-3% of patients at various time points throughout the study (Figure 6).

Discussion

In this study, treatment with oxycodone CR was associated with a statistically and clinically significant reduction in pain scores in patients with chronic cancer or non-cancer pain refractory to NSAID therapy. Improvement in pain was as-

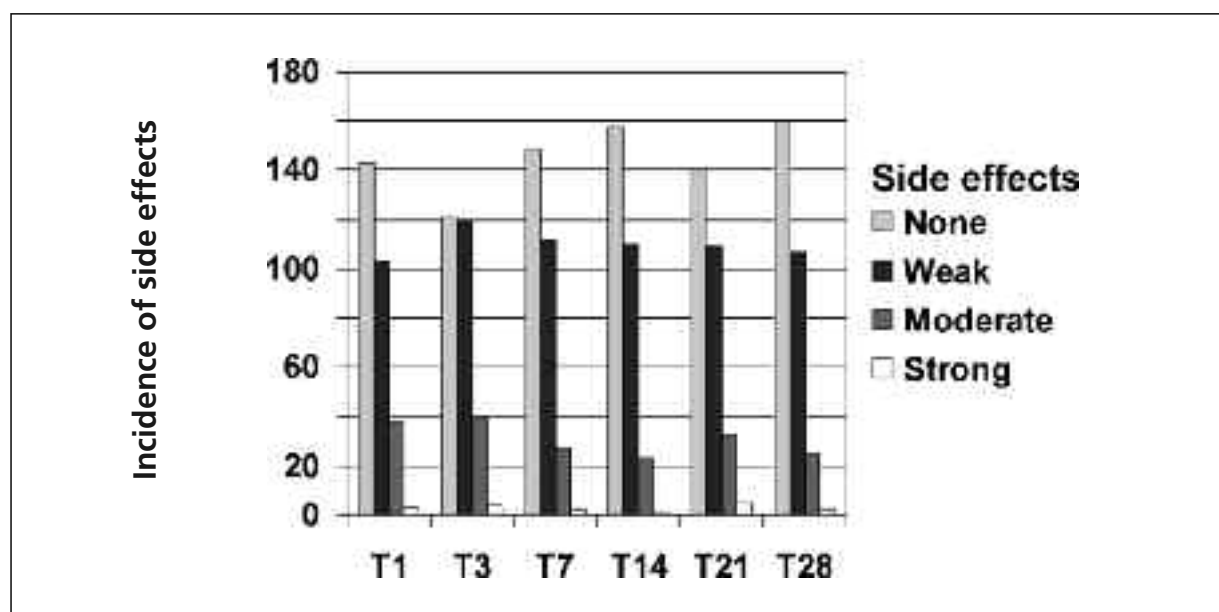


Figure 6. Incidence of side effects during the study period.

sociated with better QoL, and the majority of patients (91%) rated treatment as effective or very effective.

The WHO suggests a series of steps (the analgesic 'ladder') for the management of cancer and non-cancer pain. Using this approach, mild opioid therapy (e.g. codeine, tramadol) is added at step II for mild-to-moderate pain and a strong opioid (e.g. morphine, oxycodone, hydromorphone, fentanyl, methadone) is reserved for moderate-to-severe pain at step III⁴. However, several studies suggest that it may be appropriate to skip from the first step to the third step of the ladder by using low dosages of strong opioids. A newer approach to the WHO classification, which also provides indication for non-cancer pain, suggests the strength of the analgesic should be proportional to the intensity of the pain²⁶. The investigators acknowledge that, in addition to terminally ill patients with cancer, patients with a relatively long life expectancy can experience moderate-to-severe pain, which can impact significantly on their quality of life. In our study, where patients were experiencing moderate-to-severe pain, and who were not necessarily terminally ill, early treatment with strong opioids at low doses proved a successful alternative to the 3-step approach.

Low doses of morphine (starting at 10 or 15 mg/day) have been shown to be associated with adequate pain control during 4 weeks of treatment and a good side effect profile in opioid-naïve patients with cancer pain²¹. In addition, initiating oxycodone at a dosage of 10 mg/day has been shown to induce good analgesia in patients with cancer pain^{16,22-24}. However, one of these studies was conducted for only 7 days and in 20 Japanese patients with a mean bodyweight of 54.5 kg¹⁶.

The starting dosage of oxycodone in our study was individualised for each patient, with a mean of 11.19 mg/day, which is comparable with previous trials. While dosage titration occurred in all the studies, the beneficial effects of oxycodone on pain occur quickly, from the first day of therapy in our study, which confirms previous reports of adequate pain control within 1 day^{16,23} to 1 week²⁴ of treatment initiation.

In terms of skipping step II of the analgesic ladder, the results from this study show that initiating the strong opioid oxycodone in patients for whom NSAID therapy is not controlling pain is an effective treatment option. Another trial²⁵ has also shown that starting therapy with a strong

opioid is more effective in terms of pain control, changes in therapy and patient satisfaction than starting therapy with a weak opioid. Moreover, this study also suggested that the final dosage of strong opioids might be lower in patients initially treated with strong opioids than in those initially treated with weak opioids who progress to strong opioids. Further evidence to this fact may be provided by comparing the final oxycodone CR dose of 25.91 mg/day observed on day 28 of our study in opioid-naïve patients with 40 mg/day dose reported in the study by Silvestri et al²³ in which almost two-thirds of patients had received prior treatment with weak opioids alone or in combination with NSAIDs.

Furthermore, progressing from step I to step III in patients with chronic cancer pain has demonstrated advantages over following the traditional steps of analgesic therapy with respect to the number of days with worst pain²⁶, indicating that direct progression to step III of the WHO analgesic ladder is possible and has the potential to beneficially affect pain scores. However, the incidence of adverse events (particularly constipation) was higher in the strong opioid group and the Authors noted that while the more aggressive treatment strategy was feasible and effective, side effects would need to be carefully managed²⁶.

Adverse events are an important limiting factor in the use of morphine, with one report stating that 25% of cancer patients do not have an adequate response to morphine or experience intolerable side effects²⁷. Our study demonstrated that oxycodone CR is well tolerated with the majority of patients experiencing mild or no adverse events and <2% of patients discontinuing the drug due to adverse effects. Factors contributing to marked variability in the response to morphine include age, renal and hepatic function, concomitant medication and mechanism of pain²⁸⁻³².

Oxycodone is a good alternative to morphine because it has similar prescribing properties to morphine and, like morphine, is available in short- and long-acting formulations²⁷. In addition, the dosage conversion ratio is straightforward and it has a different metabolic pathway²⁷. As regards efficacy, oxycodone CR is supported by type A evidence (morphine evidence type C). In a systematic review of the use of oxycodone in a variety of pain indications, the CR formulation was associated with good and clinically relevant pain control throughout the 12-hour dosing interval³³. A similar analysis restricted to randomized, controlled trials in patients with cancer pain re-

ported that oxycodone had similar efficacy and tolerability to morphine, making it a suitable choice in this indication¹⁰. In the latter trial, switching patients who did not respond to, or could not tolerate, morphine to oxycodone improved the response rate from 75% to 96%²⁷.

Studies of analgesic treatment in patients without cancer have documented efficacy for oxycodone CR therapy in neuropathic pain, both alone³⁴⁻³⁶ and in combination with other agents^{13,14}. In accordance with the findings of the current study, in previous trials oxycodone CR was shown to significantly decrease pain^{13,14,35,36}, improve QoL¹⁴, and be rated as effective by patients^{14,35}. Furthermore, combining oxycodone CR with gabapentin¹³ or pregabalin¹⁴ was associated with pain relief that was superior to the traditional neuropathic pain therapies alone. Pain treatment with opioids is still relatively rare in Italy, where opioid usage per patient is the lowest in Europe. The findings from our large study show that treatment with this drug class is effective and also safe, even for non-cancer patients.

In conclusion, the results of this study demonstrate the efficacy and tolerability of oxycodone CR in patients with moderate-to-severe pain of a variety of aetiologies and confirm the feasibility and effectiveness of moving directly from step I to step III on the WHO analgesic treatment ladder. The strength of this evidence would be enhanced by replication of the study results in randomized, controlled clinical trials.

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