Efficacy and Safety of Oxycodone Injection for Relieving Cancer Pain: A Study in Japan Consisting of Two Open Trials for Intravenous and Subcutaneous Administration

Tetsusuke Yoshimoto,*a Emi Ryu,b Shiro Tomiyasu,c Minoru Hojo,d Hideya Kokubun,e and Motohiro Matoba,f

*aDepartment of Palliative and Supportive Care, Chukyo Hospital; 1-1-10, Sanjo-cho, Minami-Ku, Nagoya, Aichi 457-8510, Japan: bDepartment of Hospital Pharmacy, Nagasaki University Hospital; 1-7-1, Sakamoto, Nagasaki, Nagasaki 852-8501, Japan: cDepartment of Palliative Care, Sasebo City General Hospital; 9-3, Hirase-cho, Sasebo, Nagasaki 857-8511, Japan: dPresident, Dejima Hospital; 12-23, Dejima-cho, Nagasaki, Nagasaki 850-0862, Japan: eDepartment of Pharmacy, Tokyo University of Pharmacy and Life Sciences; 1432-1, Horinouchi, Hachioji, Tokyo 192-0392, Japan: fDepartment of Palliative Care, Japanese Red Cross Medical Center; 4-1-12, Hiroo, Shibuya-ku, Tokyo 150-8935, Japan.

*To whom correspondence should be addressed.

e-mail: yoshimoto-tetsusuke@chukyo.jcho.go.jp
Summary

Pure oxycodone injection became increasingly necessary after oral oxycodone was launched in Japan in 2003. However, trials clarifying the efficacy and safety of injection are rare. Therefore, a multicenter open study on injection was designed and carried out in 2010, resulting in the launch of injection therapy in 2012. As published domestic case reports on efficacy already show widespread prescription, this study aimed to provide useful information for cancer pain relief in Japan and other countries. Our oxycodone injection study consisted of two trials, one of intravenous (S#9131) and the other of subcutaneous (S#9132) administration. The minimum required number of enrolled patients suffering cancer pain was determined to be 70 in S#9131 and 20 in S#9132. These studies had the same dose-titration protocol as the main endpoint, i.e. pain relief rate (PRR) defined as the rate of achieving adequate pain control (APC), as in prior oral oxycodone trials in Japan. In S#9131, PRR was 81.4% (95% confidence interval: 70.3%-89.7%), therefore, the null hypothesis of PRR < 70% was rejected using the binominal one-sided test ($p=0.0217$). In S#9132, PRR was 73.7% also surpassing 70%. Safety was also assessed in the same way as in prior trials. The majority of adverse effects were moderate or mild and recovered with no sequelae. As shown above, the injection was considered to be effective and safe in cancer pain treatment. The details of these trials, particularly the dose-titration protocol for achieving APC and route switching information, are expected to enhance injection convenience for prescribers.

Key words cancer pain; pain management; oxycodone; opioid switching; route switching
Cancer pain has a high prevalence throughout the disease course\textsuperscript{1,2}. For cancer patients and their families, pain is among the most feared\textsuperscript{3,4} and distressing\textsuperscript{2} symptoms. Thus, pain relief should be achieved with gold-standard therapy, according to the World Health Organization (WHO) guidelines, with drug treatment as the mainstay,\textsuperscript{5} and opioids are generally recognized as a vital part of achieving pain relief.\textsuperscript{6} The guideline cites oxycodone as a key drug.\textsuperscript{5} In Japan, oral oxycodone has been available as a controlled-release tablet since 2003 and as an immediately-released powder since 2007, surpassing morphine in domestic consumption by over two-fold in the three years after 2011.\textsuperscript{7} The vast majority of opioid prescriptions against cancer pain are oral formulations,\textsuperscript{8} and oxycodone is already playing a vital role in cancer pain treatment in Japan. The demand for parenteral oxycodone has been rising rapidly because considerable numbers of patients with cancer are often forced to stop oral administration due to nausea and vomiting (e.g., ileus or anticancer therapy), difficulty swallowing (e.g., advanced head-and-neck cancer, or severe weakness), which can cause severe pain that is not controllable with oral opioids.\textsuperscript{9-11} For improvement of pain control,\textsuperscript{10,11} route switching from oral to intravenous is a commonly employed method.\textsuperscript{9} However, in Japan in 2008, the alternatives for injection of strong opioids to relieve moderate or severe pain were limited to morphine, fentanyl and oxycodone compounds.

In Europe, parenteral oxycodone was the main treatment for acute postoperative pain starting in 1917.\textsuperscript{12} In Japan as well, compound oxycodone injection (OXJ) became available chiefly for postoperative management starting in the 1920s. However, since the efficacy and safety of this drug for cancer pain have only been compared with those of compound injection formulations, as demonstrated only in audit studies,\textsuperscript{13,14} its official use is limited to subcutaneous administration. The compound agent hydrocotarnine, a non-narcotic opium alkaloid, is among the most important but can cause respiratory depression.\textsuperscript{15}

Given these circumstances, the Japanese Society for Palliative Medicine submitted a
request for developing pure OXJ to the exploratory committee on unapproved medicine in the Ministry of Health, Labour and Welfare of Japan. At that time in Japan and other countries, such an agent had not yet been adequately examined to determine its efficacy and safety in cancer pain treatment by means of a clinical trial. As we assumed that the present study could well provide substantial benefits to patients in need of cancer pain therapy in Japan and other countries, we designed a protocol in 2009 and carried out the study in 2010. This study consisted of the two open-trials, one of intravenous (coded S#9131) and the other of subcutaneous (coded S#9132) OXJ, employing the same titration protocol, endpoints and safety assessment as prior trials of oral oxycodone in Japan.\textsuperscript{16,17}

Following completion of these trials, OXJ was approved and then launched in 2012.\textsuperscript{18} As several cases suggesting the usefulness of OXJ have already been reported,\textsuperscript{19-21} documenting the details of the trials conducted herein is anticipated to provide useful information to Japanese medical personnel treating cancer pain. In addition, as there are minimal if any ethnic differences in oxycodone-metabolizing capacities,\textsuperscript{22} we believe that our results would also be useful to practitioners in other countries.

PATIENTS AND METHODS

Patients The two trials (S#9131 of intravenous OXJ; S#9132 of subcutaneous OXJ) were conducted for in-patients suffering from cancer pain in 23 Japanese hospitals which had at least one highly experienced physician specializing in cancer pain treatment. The study period was January to December of 2010.

The inclusion criteria were any of the following conditions: 1) patients who had been prescribed strong opioids, defined as “opioid tolerant,” and 2) patients suffering from moderate or severe cancer pain without opioid prescription, defined as “opioid naïve.” Pain intensity was evaluated according to a patient-rated, four-point categorical scale, namely the

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CAT scale (0: no pain, 1: slight pain, 2: moderate pain, 3: severe pain).23)

Enrollment was permitted when the patients met all of the following conditions: 1) age > 19, 2) able to maintain a written patient diary, 3) route accessible for continuous injection in each trial. Exclusion criteria were 1) contraindications for opioid administration, 2) liver or renal dysfunction rated > Grade 3 of CTCAE v3.0 -JCOG,24,25) 3) scheduled to undergo painful procedures possibly affecting the evaluation, 4) scheduled to receive chemotherapy as the first regimen, 5) prescribed two or more opioids, 6) participation in another trial during the prior three months, 7) pregnant or possibly pregnant, or nursing, 8) taking oral oxycodone just in S#9132 trial, designated to evaluate OXJ pharmacokinetics.18) The only exception was for pharmacokinetic analyses of OXJ conducted for another study.

Endpoints The primary endpoint in both trials was the Pain relief rate (PRR). PRR and its titration procedure were the same as those of prior oral oxycodone trials.16,17) The PRR of the trials was defined as the rate of patients achieving adequate pain control (APC) among all of the evaluable patients on Day 1 (Fig. 1). Every morning throughout the trials, the institutional responsible physician (IRP) determined whether APC had been achieved. When the patients achieved APC (on Day $\alpha$ in Fig. 1), even if an OXJ dose increase was needed after that day, they were not excluded from our PRR population. Along with PRR, the mean value of all of the dates that APC had been achieved (Day $\alpha$) was calculated, and these dates clearly ranged from 3 to 7 according to the APC definition shown in Fig. 1. In addition, to estimate the effects of the previously prescribed opioids on PRR, the PRR was calculated separately for each opioid.

The secondary endpoints were: 1) baseline pain intensity for the past 24 hours until 8 a.m., rated according to the four-point CAT scale or 100 mm Visual Analogue Scale (VAS; 0: no pain – 100: worst pain imaginable), 2) the five-point satisfaction scale for OXJ (1: very
poor, 2: poor, 3: fair, 4: good, 5: excellent) along with the oral oxycodone trials, and 3) the
efficacy of OXJ for breakthrough pain, rated by pain intensity reduction from just before
infusion until the designated time point after infusion (10 minutes for intravenous and 20
minutes for subcutaneous administration).

All of these measures were evaluated by aggregation of the data from the original
and self-recorded patient diaries, along with which all adverse events (ADEs) were also
tallied.

Study design

Sample size designation

First, the sample size for the intravenous trial (S#9131) was calculated. After rejecting the
null hypothesis that the PRR of the injection is equal to 70% (minimum results of oral
oxycodone trials ranged from 69.1% to 91.4%), the true PRR was assumed to be 85% based
on the general rule that injection agents have high bioavailability. Under this assumption, the
number of patients needed to reject the null hypothesis using the binomial test with more than
80% power with a one-sided significance level of 0.025 was calculated to be more than 60.
Assuming a 15% of drop-out rate, 70 patients were to be enrolled in this study.

Second, for the subcutaneous trial, S#9132: three studies had already demonstrated
the efficacy and safety of compound oxycodone injection for cancer pain in Japan.13,14,26) Therefore, instead of testing a hypothesis, we evaluated the first and second outcomes of the
oral oxycodone trials. The necessary sample size was determined to be 20 cases for analyzing
the pharmacokinetics of OXJ, as described in our 2014 publication.18)

Study agent  The study agent, coded as OXJ in the trials, was the injectable
product containing oxycodone hydrochloride at a concentration of 10 mg/ml. The ampules

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were available in two sizes of 1 ml and 5 ml, supplied by Shionogi & Co., Ltd. As OXJ injectors, the syringe drivers available at the hospitals participating in these trials were used.

**Titration procedure**  The baseline dose of OXJ on the starting date (Day 0 in Fig. 1) was: 1) for the opioid-tolerant patients, the OXJ dose equipotent with those of previously prescribed strong-opioids using the uniform conversion ratios†. 2) for the opioid-naive patients, a uniform dose of 10 mg/day. The OXJ rescue doses were set as the one-hour dose of the baseline doses for relieving breakthrough pain27) or baseline pain flare.28) The designated minimum interval of rescue injections was set at 10 minutes for intravenous and 20 minutes for subcutaneous administration.

On Days 1 through 6 only, raising the baseline doses was permitted by approximately 1.25 to 1.5 fold as needed, and these increments were limited to once a day and it was requested that at least one of the following conditions be met: 1) intensity of baseline pain > mild, 2) rescue-doses injected > twice a day, or 3) other rational reasons as determined by the physician in charge. In light of the Good Clinical Practice (GCP) guidelines, when the sum of rescue doses in a day and the baseline dose surpassed the baseline dose, the baseline dose was permitted to be increased by 1.5 to 2.0 fold. OXJ dose escalation was prohibited on both Day 0 and Day 7, such that the maximum time period for baseline-dose escalation was 6 days.

All of the patients who completed the trials were allowed to choose whether to switch OXJ to other strong opioids, or to continue OXJ as another durability trial (S# 9133). More specifically, as shown in Fig. 1, all patients chose on day 7, whether to receive treatment with another opioid equipotent with the OXJ prescribed or to continue OXJ as S# 9133.

†Oral oxycodone: OXJ = 4:3; Oral morphine: OXJ = 2:1; Compound oxycodone
injection: OXJ = 1:1; Injection morphine: OXJ = 4:5; Injection fentanyl: OXJ = 1:62.5; Dose of transdermal fentanyl released per hour: OXJ = 1:1000

Other than the ratio converted on the basis of the compound oxycodone injection, practical adjustment of these ratios by <20% was permitted.

**Safety and good practice**  When intolerable ADEs were observed, reduction of the baseline doses to approximately one-quarter of the original dose was permitted, and these reduction rates and the number of times per day had no safety limitations. Both discontinuing the trials and supplying appropriate alternative treatments were also permitted, if the patients showed a minimal likelihood of achieving APC, the number of times that rescue doses were needed was too high, or subjects lost the ability to understand the trials.

**Protocol violation**  Any of the following was regarded as a protocol violation: 1) any other opioid analgesic was prescribed concomitantly, 2) newly prescribed non-opioid, adjuvant drugs or changes in drug regimens. When the IRP evaluations were conducted on at least one day, the patients with these violations were also included in the PRR calculation and safety assessment.

**Ethical issues**  This study was conducted in accordance with the ethics standards of the Declaration of Helsinki and GCP guidelines. All patients participating in the trials provided written informed consent prior to study enrollment, and the trials received ethics approval from the institutional review boards of all 23 hospitals.

**Safety assessment**  The safety of OXJ was evaluated taking into consideration both the severity and the frequency of ADEs throughout the present trials from Day 0 to Day 7.

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The severity was rated according to CTCAE v3.0 (Grade 1: mild, Grade 2: moderate, Grade 3 or higher: severe). Information on ADEs associated with OXJ was collected from the patient diaries and designated laboratory tests, and then aggregated. The Protocol was designed to grade the relationships between each ADE and OXJ, using a 4-point scale (definitely related; probably related; possibly related; not related). An adverse effect (AE) was defined as an ADE graded as definitely, probably or possibly related. The AEs with incidences >10% were defined as Common AEs, following the protocol of an earlier oral oxycodone trial.

**Statistical analysis**  
Before-and-after studies on pain-intensity and patient-acceptability factors were conducted using the Wilcoxon signed-ranked test, and the 95% confidence interval (CI) was calculated employing the Clopper-Pearson method. For hypothesis testing, a binominal one-sided test using the Clopper-Pearson method with a 0.025 % CI was conducted.

All statistical analyses were carried out using the Statistical Analysis System, or SAS (version 8.2, SAS Institute Inc. NC, USA). The level of significance was set at \( p < 0.05 \).

**RESULTS**

**Patients**  
The body weights of enrolled patients (\( n=92 \)) were all roughly 50 kg (Table 1). In S#9131, one patient died on Day 1 due to rapid unexpected progression of a malignancy, and another patient was also withdrawn because of paraplegia onset before starting OXJ treatment. In S#9132, one patient died on Day 1, and this death was judged to be due to unexpectedly rapid growth of metastases. Ultimately, 70 of 72 patients in S#9131, and 19 of 20 patients in S#9132 were evaluable and were thus included in our efficacy analysis.

As to baseline pain intensity at study initiation, the rates of patients with moderate or
severe pain were 55.7% (39 of 70) in S#9131, and 47.4% (9 of 19) in S#9132.

**Endpoint evaluation**  In S#9131, for the primary endpoint, the achievement ratio of pain relief evaluated according to the PRR was 81.4% (57 of 70; 95% CI: 70.3%-89.7%), such that the null hypothesis of PRR <70% was rejected using the binominal one-sided test ($p=0.0217$). In study #9132, the achievement ratio of pain relief was 73.7% (14 of 19), which also surpassed 70%.

PRR according to each category of the most potent analgesics administered just before starting OXJ are shown in Table 2. In S#9131, PRR according to prior oral oxycodone and transdermal fentanyl accounted for approximately 75% (43 of 58 opioid-tolerant) of cases, and, in S#9132, transdermal fentanyl accounted for approximately 65% (11 of 17 opioid-tolerant) of cases. When the prior opioids were limited to morphine injection, the calculated PRR was 62.5% (< 70%) in S#9131, though the CI was much wider.

Before-after analyses, consisting of baseline pain intensity and patient satisfaction, were conducted on the two secondary-endpoints of both OXJ trials (Table 3). In S#9131, pain intensity rated by both CAT scale and VAS, as well as patient satisfaction rated by the 5-point satisfaction category, showed statistically significant improvement. However, the results of the improvement assessment of S#9132 did not reach statistical significance ($p=0.136$) for the patient satisfaction scale, while achieving PRR at an appropriate rate (> 70%) was associated with significant improvement of VAS ($p=0.0061$) and approached statistical significance ($p=0.058$) for CAT.

As one of the three secondary-endpoints, the efficacy of OXJ as a rescue medication was also evaluated employing before-after analysis focusing on the right-now-pain intensities, comparing just-before-infusion versus at the-designated-time-after-infusion, which showed that OXJ infusion decreased pain intensity from $2.0 \pm 0.6$ to $1.1 \pm 0.7$ in S#9131, and from...
2.1 ± 0.7 to 1.2 ± 0.8 in S#9132, showing statistically significant ($p<0.0001$) reductions in both trials. The rescue medication was administered 383 times in 70.0% (49 of 70 subjects) of S#9131 participants, and 105 times in S#9132 (11 of 19 subjects). One episode, in S#9132, could not be evaluated due to a missing record.

**Base-dose titration**  Changes in daily basal doses of OXJ (mg/d) from Day 1 to 7 (Fig. 1) were computed as the average ± standard deviation (median): from 38.5±46.5 (18.7) to 88.1 ± 179.7 (32.0) in S#9131, and from 53.7 ± 63.7 (23.6) to 87.6 ± 135.7 (27.3) in S#9132. For the opioid-tolerant cases in both trials particularly, the OXJ basal doses (mg/d) were compared from the day before starting the trial until the day before completion, aiming to evaluate the OXJ titration process as the mean ± SD (median). The comparisons were as follows: in 58 of those receiving S#9131, the change was from 36.9 ± 86.2 (22.8) to 113.0 ± 186.1 (41.8); in 17 of the S#9132 trial participants, the change was from 52.6 ± 64.5 (34.1) to 86.4 ± 138.6 (28.3).

In the majority of cases, on the day that APC was achieved, the OXJ doses needed were <50 mg/day: 68.5% (48 of 70) in S#9131 and 63.2% (12 of 19) in S#9132. When these values were computed for opioid-naïve patients only in both trials, all of the OXJ doses needed to achieve APC were <50 mg/day (12 of 12 in S#9131 and 2 of 2 in S#9132). On the other hand, a few patients, 14.2% (10 of 70) in S#9131 and 5.3% (1 of 19) in S#9132, needed 250 mg/day or even higher doses on the day that APC was achieved.

**Safety** Three hundred and eighty-seven ADEs (Adverse Events) and 147 AEs (Adverse Effects) were reported in the two trials. The ADE incidence was 95.8% (69 of all 72 cases enrolled; 95% CI: 88.3-99.1) in S#9131, and 95.0% (19 of all 20 cases enrolled; 95% CI: 75.1-99.9) in S#9132. The AE incidence based on IRP judgments accounted for 59.7%
The severe AE (≥ Grade 3 of CTCAE scale) incidences were as follows: First, in the S#9131 trial participants, the incidence of severe AEs (≥ Grade 3 of the CTCAE scale), other than one death caused by unexpectedly rapid tumor growth, due to OXJ was reported to be 16.9% (12 of 71 patients, 12 episodes), including eight patients with constipation (11.3%), two with somnolence (2.8%), and two with delirium (2.8%). All of the severe AEs caused by OXJ were tolerable and recovery was achieved, except in case given OXJ who was withdrawn from the study due to rapidly progressing paraplegia attributable to the tumor itself, by administering supportive therapies and reducing the OXJ dose. Second, in the S#9132 trial participants, the incidence of severe AEs due to OXJ was reported to be 15.8% (3 of 19 patients, 3 episodes), including three patients with constipation (3 of 19, 15.8%) and one with somnolence (1 of 19, 5.3%), and recovery from all of these AEs was achieved with supportive therapy and none of the patients required withdrawal of OXJ.

Common AEs, i.e. those with an incidence >10%, were as follows: 20.8% for lethargy, 18.1% for constipation and nausea, and 15.3% for vomiting in S#9131; 35.0% for skin erythema at the injection site, 30.0% for lethargy, constipation and nausea, and 25.0% for vomiting in S#9132. In contrast, laboratory data abnormalities were relatively rare: proteinuria increment (4.2%), serum alkaline phosphatase elevation (2.8%), and blood urea nitrogen (BUN) elevation (1.4%) in S#9131; hemoglobin decrement (5.0%) and BUN elevation (5.0%) in S#9132. In addition, these abnormal laboratory values could not be defined as AEs, because tumor effects and concomitant medications were presumably responsible for the observed changes, and the majority of these values were normalized after discontinuation of OXJ administration.

It is noteworthy that the patients with the longest exposure to OXJ accounted for 90.3% (65) of S#9131 trial participants and 80.0% (16) of the S#9132 trial participants.
Furthermore, none of the patients described severe AEs in their diaries. Several, 18 (27.7%) in the S#9131 trial and 6 (37.5%) in the S#9132 trial, chose to continue OXJ administration rather than switching to another regimen (trial, S#9133).

**DISCUSSION**

To the best of our knowledge, the present study consisting of two OXJ open-type trials employing intravenous and subcutaneous routes is the first multicenter investigation to clarify the efficacy and safety of OXJ in cancer patients with moderate or severe pain. The prior studies on OXJ for cancer pain aimed to clarify its pharmacokinetics, to evaluate the attenuation of AE by opioid switching to OXJ, or to estimate the conversion ratio between morphine and oxycodone.

We obtained three major findings. First, the efficacy of intravenous or subcutaneous OXJ was confirmed, with statistical significance, to not be inferior to that of oral controlled-release oxycodone; PRR (81% in S#9131; 76.5% in S#9132) was similar to the PRR obtained in oral oxycodone trials [69.1% reported by Takeda et al. and 90.0% by Koizumi et al.]. In S#9131 particularly, the minimum-efficacy level (PRR >70%) and the mandatory sample size for statistical hypothesis testing (n=70) were set prospectively. Second, the two trials employed the same titration and evaluation methods as preceding trials on oral oxycodone, a drug which has long played a major role in treating cancer pain in Japan. Third, in both trials, it was shown that OXJ is effective for not only baseline pain but also breakthrough pain, the management of which plays a key role in improving quality of life for patients suffering from cancer pain. Fourth, though more research is needed, the present OXJ trials provide useful safety data to physicians and pharmacologists in our country managing cancer pain. This information facilitates predicting severe AEs and optimizing its management.
The major findings of this study suggest that the vast majority of Japanese cancer patients treated with oral oxycodone could be switched to the injection form of OXJ, easily and safely, whenever needed. Our results also suggest OXJ to be an optimal form of administration in opioid-naïve patients.

The S#9132 trial participants showed no significant improvement of the patient satisfaction scale, though achieving PRR at an appropriate rate (> 70%) with significant improvement of VAS was observed in this trial. It is noteworthy that, although OXJ was found, in our prior population analysis,\textsuperscript{18} to show no pharmacokinetic differences in terms of clearance (CL) between intravenous and subcutaneous infusion, this trial yielded seemingly conflicting results.

We speculate that the poor satisfaction score improvement in the S#9132 trial participants is attributable to one or more of the following factors: 1) the pain associated with subcutaneous injection is influenced by both the volume and the type of drug\textsuperscript{36}. Thus, patients in the S#9132 trial might have suffered discomfort and refused dose increments (particularly of frequent rescue bolus administrations). In particular, the majority, 52.6% of the S#9132 participants, had good ECOG PS of 0 or 1. As good PS may exacerbate skin irritation\textsuperscript{37}, such patients might be susceptible to skin irritation. Non-metal needles are superior to butterfly needles in suppressing skin irritation and may thereby allow continuous subcutaneous infusion\textsuperscript{38}, but our protocol had no restrictions on the selection of needles for use. 2), while in the # 9131 (25.7%) trial, the opioid given previously in the S#9132 trial was, by coincidence, usually transdermal fentanyl (64.7%). Therefore, on the day of starting administration or early in the period of receiving S#9132, opioid switching itself may have resulted in cancer pain recrudescent due to incomplete cross tolerance beyond the conversion rate designated in our trials\textsuperscript{39}. Furthermore, the base dose escalation of OXJ was inhibited and AEs (e.g., lethargy and constipation) increased, because patients were switched to
fentanyl, a highly selective agonist of the mu receptor to OXJ as a multi-receptor agonist of mu, kappa and lambda receptors.

It is noteworthy that, although not intended, more than 80% of the enrolled patients in these two trials were opioid tolerant. As the enrollment condition for opioid-tolerant patients, they had to have been receiving opioid treatment for at least two weeks, on average. Therefore, pain experienced in these two trials was presumably more refractory than that in prior oral oxycodone trials [all subjects were opioid naïve in the trials of Koizumi et al.\(^{16}\) and Takeda et al.\(^{17}\)]. Furthermore, refractoriness to opioid therapy was presumably resolved by opioid switching and/or route switching. Cancer pain relief using OXJ is assumed to be achieved by appropriate application of a titration protocol and close observation for ADEs by physicians experienced with cancer pain treatment. In a sense, the implementation of trials may result in facilitating utilization of the two principles, “for the individual” and “with attention to detail”, advocated in the WHO pain relief guidelines.\(^5\) A multicenter audit focusing on palliative care teams in Japan suggested that these two principles are the cornerstones of relieving pain in cancer patients seeking consultation.\(^{40}\) When the symptoms or AEs of prior opioids (e.g., lethargy or constipation) are difficult to manage, opioid switching might be a good treatment option in selected patients.\(^{29}\)

The present study has several limitations. First, patients enrolled in these studies might have particular forms or levels of pain anticipated to be highly responsive to OXJ with few AE. This is because highly skilled IRPs dealing with cancer pain treatment might well be expected to make an informed choice as to whether a potential subject should be enrolled in the study or not. Second, even when the information pertaining to rescue medication was unified, the number of times that a rescue dose of OXJ was needed might be reduced not only due to the analgesic effect of the basal OXJ dose, but also by efforts aimed at supporting patients in their daily activities and thereby preventing or reducing breakthrough pain. The
skills with which such efforts are made would likely increase as the trial proceeded. Third, the OXJ efficacy evaluation was limited during the first week. Along with the assessment schedule of the interventions performed by the hospital palliative care team, we limited the evaluation phase to one week by design, and this was regarded as an avoidable limitation because worsening of pain is often observed as the disease progresses or new symptoms manifest. Fourth, no patients prescribed weak opioids were enrolled and there were very few opioid-naïve patients (17.1% in S1; 10.0% in #9132) in the present study. In particular, although the necessity of the second step of the WHO analgesic ladder is still controversial, we advocate that the efficacy of opioid switching from weak opioids to OXJ be explored in a future study.
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Conference proceedings  The authors gave a poster presentation at the 12th Congress of the European Association for Palliative Care (EAPC), Lisbon, Portugal in 2011.

Conflict of Interest  The authors declare no conflict of interest.
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**Figure legends**

Fig. 1. Overview of the OXJ study consisting of two trials: intravenous (S#9131) and subcutaneous (S#9132).

When adequate pain control (APC) was achieved on Day \( \alpha \), the day of APC achievement was defined as \( \alpha \), which is the number of days required to achieve APC. The Pain Relief Rate, the main endpoint of the present study, was the percentage of patients achieving APC among all of the patients evaluable on Day 1. The secondary endpoint was the mean with standard deviation value of all of the days needed to achieve APC (the values of \( \alpha \) for all subjects)

OXJ, Oxycodone injection; CAT scale, Categorical scale.
Adequate pain control (APC) was not achieved until Day α evaluation when the following five conditions were first met for more than 48 hours, according to the APC definition.

- No need for escalation of OXJ daily basal dose
- “0: No” or “1: Slight” in pain rating by 4-point CAT scale
- Rescue-dose given no more than twice per 24hr.
- No change in dose or regimen of analgesics except OXJ
- All adverse events reported as “tolerable”
### Table 1. Demographics and cancer-related information on all patients (FAS, n = 89)

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<th>Study #9132 Subcutaneous injection (n = 19)</th>
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</tr>
<tr>
<td>Liver function: ALT (IU/l)</td>
<td>28.7 ± 35.4 (5 to 175)</td>
<td>33.3±25.2 (9 to 111)</td>
</tr>
<tr>
<td></td>
<td>AST (IU/l)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34.1 ± 34.1 (10 to 171)</td>
<td>28.3 ± 21.5 (11 to 112)</td>
</tr>
<tr>
<td>% patients of CAT(^a) pain intensity, total (opioid-naïve, opioid-tolerant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12.9 (0.0, 12.9)</td>
<td>10.5 (0.0, 10.5)</td>
</tr>
<tr>
<td>1</td>
<td>31.4 (0.0, 31.4)</td>
<td>42.1 (0.0, 42.1)</td>
</tr>
<tr>
<td>2</td>
<td>45.7 (14.3, 31.4)</td>
<td>31.6 (10.5, 21.1)</td>
</tr>
<tr>
<td>3</td>
<td>10.0 (2.9, 7.1)</td>
<td>15.8 (0.0, 15.8)</td>
</tr>
</tbody>
</table>

\(^a\)Categorical scale: 0: no pain, 1: slight pain, 2: moderate pain, 3: severe pain (>2 weeks).
FAS, full analysis set; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Table 2. Pain relief rate (PRR) according to prior analgesics

<table>
<thead>
<tr>
<th>Most potent analgesic prescribed at registration</th>
<th>Study #9131</th>
<th>Study #9132</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous injection</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td></td>
<td>(n = 70)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>PRR (95% CI)</td>
<td>Patients (%)</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>70 (100.0)</td>
<td>81.4 (70.3–89.7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-opioid</td>
<td>12 (17.1)</td>
<td>83.3 (51.6–97.9)</td>
</tr>
<tr>
<td>Strong opioid</td>
<td>58 (82.9)</td>
<td>81.0 (68.6–90.1)</td>
</tr>
<tr>
<td>Oral oxycodone</td>
<td>25 (35.7)</td>
<td>80.0 (59.3–93.2)</td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>18 (25.7)</td>
<td>83.3 (58.6–96.4)</td>
</tr>
<tr>
<td>Morphine injection</td>
<td>8 (11.4)</td>
<td>62.5 (24.5–91.5)</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>5 (7.1)</td>
<td>100.0 (47.8–100.0)</td>
</tr>
<tr>
<td>Fentanyl injection</td>
<td>1 (1.4)</td>
<td>100.0 (–)</td>
</tr>
<tr>
<td>Oxycodone compound injection</td>
<td>100.0 (–)</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>a</sup>Number of days required for pain relief, mean ± SD: 4.3 ± 1.4

<sup>b</sup>Number of days required for pain relief, mean ± SD: 3.8 ± 1.1

CI, confidence interval; SD, standard deviation.
Table 3. Efficacy evaluation of oxycodone injection by before-after comparison of three secondary endpoints of baseline pain rating in intravenous administration (Study S#9131) and subcutaneous administration (Study S#9132) groups

<table>
<thead>
<tr>
<th></th>
<th>CAT&lt;sup&gt;a&lt;/sup&gt;</th>
<th>VAS&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Patient satisfaction&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The day</td>
<td>The day</td>
<td>The day</td>
</tr>
<tr>
<td></td>
<td>before</td>
<td>before</td>
<td>before</td>
</tr>
<tr>
<td></td>
<td>starting</td>
<td>completion</td>
<td>p value</td>
</tr>
<tr>
<td>Study #1931</td>
<td>1.5 ± 0.8</td>
<td>0.8 ± 0.7</td>
<td>&lt; 0.0001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>(n = 70)</td>
<td>(0 to 3)</td>
<td>(0 to 3)</td>
<td></td>
</tr>
<tr>
<td>Study #1932</td>
<td>1.5 ± 0.9</td>
<td>1.0 ± 0.9</td>
<td>0.0578†</td>
</tr>
<tr>
<td>(n = 19)</td>
<td>(0 to 3)</td>
<td>(0 to 3)</td>
<td></td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD with range.

<sup>a</sup> Four-point categorical (CAT) scale (0: no pain, 1: slight pain, 2: moderate pain, 3: severe pain).

<sup>b</sup> Visual analogue scale of 100-mm horizontal (left end: no pain, right end: worst pain imaginable).

<sup>c</sup> Five-point patient satisfaction scale (1: very poor, 2: poor, 3: fair, 4: good, 5: excellent).

Statistical analysis was performed between the scales obtained on the days before the start and the completion of both trials using the Wilcoxon signed-rank test. *Statistically significant (p < 0.05). †Improvement but without statistical significance (p < 0.06).

VAS, Visual Analogue Scale.