Regular Article

A Clinical Study on Administration of Opioid Antagonists in Terminal Cancer Patients: 7 Patients Receiving Opioid Antagonists Following Opioids among 2443 Terminal Cancer Patients Receiving Opioids

Yoshihiro Uekuzu,*[a,b] Takashi Higashiguchi,[b] Akihiko Futamura,[a,b] Akihiro Ito,[b] Naoharu Mori,[b] Miyo Murai,[b] Hiroshi Ohara,[b] Hiroko Awa,[b] and Takeshi Chihara[c]

[a] *Department of Pharmacy, Fujita Health University Nanakuri Memorial Hospital; 424–1 Oodori, Tsu, Mie 514–1295, Japan:* [b] *Department of Surgery and Palliative Medicine, School of Medicine, Fujita Health University; 1–98 Dengakugakubo, Kutsukake, Toyoake, Aichi 470–1192, Japan: and* [c] *Division of Biochemistry, Fujita Memorial Nanakuri Institute, Fujita Health University; 423 Oodori, Tsu, Mie 514–1296, Japan.*

Received September 6, 2016; accepted December 6, 2016; advance publication released online December 16, 2016

There have been few detailed reports on respiratory depression due to overdoses of opioids in terminal cancer patients. We investigated the situation of treatment with opioid antagonists for respiratory depression that occurred after administration of opioid at optimal doses in terminal cancer patients, to clarify pathological changes as well as causative factors. In 2443 terminal cancer patients receiving opioids, 7 patients (0.3%) received opioid antagonists: 6, morphine (hydrochloride, 5; sulfate, 1); 1, oxycodone. The median dosage of opioids was 13.3 mg/d, as converted to morphine injection. Respiratory depression occurred on this daily dose in 4 patients and after changed dose and route in 3 patients. Opioids were given through the vein in 6 patients and by the enteral route in 1 patient. Concomitant drugs included nonsteroidal anti-inflammatory drugs in 3 patients and zoledronic acid in 2 patients. In morphine-receiving patients, renal functions were significantly worsened at the time of administration of an opioid antagonist than the day before the start of opioid administration. These findings indicate that the proper use of opioids was safe and acceptable in almost all terminal cancer patients. In rare cases, however, a risk toward respiratory depression onset is indicated because morphine and morphine-6-glucuronide become relatively excessive owing to systemic debility due to disease progression, especially respiratory and renal dysfunctions. At the onset of respiratory depression, appropriate administration of an opioid antagonist mitigated the symptoms. Thereafter, opioid switching or continuous administration at reduced dosages of the same opioids prevented the occurrence of serious adverse events.

Key words terminal cancer patient; opioid antagonist; respiratory depression; morphine; opioid

In recent years, Japanese affected with cancer and those dying of cancer have increased and will further increase in number.[1)] Terminal cancer patients are likely to suffer from various symptoms such as pain and dyspnea.[2)] Opioids are effective for mitigation of these symptoms, unless used inappropriately.[3)] The appropriate usage of opioids is very important, because cancer cachexia will deteriorate the systemic condition in terminal cancer patients, and may reduce hepatic and renal functions involved in drug metabolism and excretion; eventually, the opioid level in blood will be relatively elevated, which may induce serious adverse events including respiratory depression.[4,5)] When respiratory depression is clinically evident, it may become fatal; therefore, an opioid antagonist will be administered if needed.[6)] Previous studies demonstrated that risk factors for opioid-induced respiratory depression included opioid overdose, advanced age, sleep apnea, chronic obstructive pulmonary disease, congestive heart failure, renal failure, and hemodialysis/peritoneal dialysis.[7–14)] However, the patients in these studies were not terminal cancer patients. In general, opioids rarely induce serious respiratory depression, when used properly in the treatment of pain relief.[12,15)] To our knowledge, there are only case reports available demonstrating the administration of opioid antagonists in terminal cancer patients for whom opioids are frequently used to mitigate symptoms other than pain.[5)] Therefore, the details remain to be elucidated, and also the incidence of respiratory depression due to overdoses of opioids in terminal cancer patients is not known. The primary objective of this study was to investigate the manifestation of respiratory depression and treatment with opioid antagonists in terminal cancer patients who had received optimal doses of opioids for mitigation of symptoms and to clarify the pathological changes as well as causative factors.

PATIENTS AND METHODS

Subjects In total, 2680 terminal cancer patients had been admitted to the palliative care unit of the Fujita Health University Nanakuri Memorial Hospital between April 1, 2004, and March 31, 2015, of which 2443 (91.2%) who had received pharmacotherapy with opioids participated in this study. Opioids had been given at optimal doses to mitigate symptoms. In this study, opioid-induced respiratory depression was suspected in 17 patients. Among those, 7 patients (0.3%) were treated by using opioid antagonists (naloxone and levallorphan); then, they were closely examined (Fig. 1). An opioid antagonist was given when respiratory rate became <8 breaths/min and coma or consciousness disturbance (that had never been observed before the onset of respiratory depression) occurred concurrently with manifestation of cyanosis, or when cyanosis alone developed.[6)] In addition, when opioid-induced respiratory depression was evaluated as life-threatening, which is contrary

* To whom correspondence should be addressed. e-mail: yuekuzu@fujita-hu.ac.jp

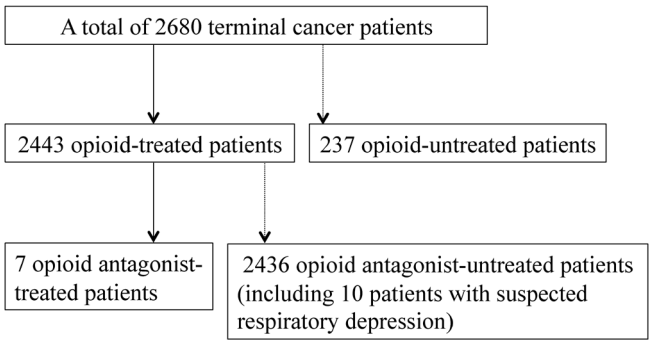

Fig. 1. Flow Chart of Study Patients

Study duration: April 1, 2004 to March 31, 2015.

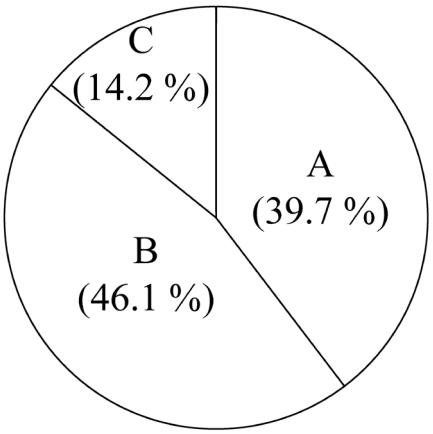

Fig. 2. Combination Therapy with Opioids in This Study (n=2443)

A: MO (n=969), B: MO+opioids (1127) (MO+OXY, 751; MO+FEN, 225; MO+OXY+FEN, 111; MO+OXY+KET, 20; MO+OXY+FEN+KET, 11; MO+KET, 8; MO+FEN+KET, 1), C: Opioids except MO (347) (OXY, 204; FEN, 112; OXY+FEN, 28; opium tincture, 2; OXY+KET, 1). Opioid switching or combination is included. MO, morphine hydrochloride, morphine sulfate; OXY, oxycodone; FEN, fentanyl; KET, ketamine.

to expected survival, opioid antagonist treatment was allowed. Administration and dosage were in accordance with the National Comprehensive Cancer Network (NCCN) guidelines and package inserts.[16–18] Prior to opioid antagonist treatment, any palliative therapies other than opioids, including radiation, nerve block, and surgical treatment, were not administered to any patients. There were no opioid antagonist-treated patients with cancer-related complications such as retention of pericardial fluid, compression of the superior vena cava, compression of the main bronchus, pneumothorax, hemothorax, infectious disease, pulmonary embolism, radiation pneumonitis, and chemotherapy-induced interstitial pneumonia. In addition, any opioid antagonist-treated patients were not associated with cancer-not-related complications, including serious respiratory disease (obstructive pulmonary disease, restrictive lung disease, or interstitial lung disease), congestive heart failure, ischemic heart disease, arrhythmia, renal failure, hepatic failure, electrolyte abnormality, and apoptosis.[19] A terminal cancer patient was defined as a cancer patient with estimated life expectancy of less than one month.[20]

Investigations We conducted a retrospective observational study. Information collection was made using electronic medical records. For opioid-receiving patients, sex, age, palliative performance scale (PPS) the day before the start of opioid administration, tumor type, the type of opioids having been used, and the type and dosage form of opioid(s) used at the time of death were checked. For opioid antagonist-treated patients, characteristics before opioid antagonist treatment were examined, including sex, age, height, weight, body mass index (BMI), PPS, tumor type; and presence or absence of lung resection, pulmonary metastasis, pleural effusion, carcinomatous lymphangitis, oxygen inhalation, ascites, hepatomegaly, and dementia.[21] It was also investigated whether opioids were combined with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, zoledronic acid, corticosteroids, hypnotic drugs, antianxiety drugs, antidepressants, antipsychotic drugs, anticonvulsants, muscle relaxants, antihistamines, β-blockers, or monoamine oxidase inhibitors. In addition, opioid administration methods (indications, type of opioid, administration route, dose, and dosing situation) before and after opioid antagonist administration, opioid antagonist administration method, and survival time after opioid antagonist administration were examined. In blood test, serum creatinine (SCr) level, estimated glomerular filtration rate (eGFR) from the SCr-based equation, aspartate aminotransferase (AST) level, and alanine aminotransferase (ALT) level were checked the day before the start of opioid administration and at the time of opioid antagonist treatment.[22] The conversion rates for opioids were based on an NCCN guidelines: for oral morphine *versus* intra venous morphine, 3 : 1; oral oxycodone *versus* intra venous oxycodone, 4 : 3; and intra venous morphine, oxycodone and fentanyl, 40 : 50 : 1.[16]

Statistical Analysis Variables following the normal distribution were expressed as the mean±standard deviation, while variables not following the normal distribution were expressed as median (interquartile range). For changes in blood test values at the start of opioid administration and after opioid antagonist treatment, the Wilcoxon signed rank test was used. JMP® Pro 11.2.1 statistical analysis software (SAS Institute, Inc., NC, U.S.A.) was used with a significance level of less than 5%.

Ethical Considerations This study was performed in accordance with the Declaration of Helsinki and its amendments, and conducted according to a protocol approved by the Ethics Review Committee of the Fujita Health University.

RESULTS

In this study, 7 patients (0.3%) in 2443 terminal cancer patients receiving opioids experienced respiratory depression but all improved by administration of opioid antagonists. There were no opioid antagonist-induced adverse events.

Characteristics of 2443 Patients on Combination Therapy with Opioids in This Study Baseline characteristics of 2443 patients who were administered opioids were as follows: 1318 males (54.0%) *versus* 1125 females (46.0%); age, 75±12 years; PPS the day before the start of opioid administration, 35 (30–40). By tumor type, 578 patients (23.7%) had respiratory tract tumors; 464 (19.0%), hepatic, cholecystic, or pancreatic tumors; 340 (13.9%), upper digestive tract tumors; 247 (10.1%), lower digestive tract tumors; 199 (8.1%), craniocervical tumors; 187 (7.7%), urologic tumors; 127 (5.2%), gynecologic tumors; 123 (5.0%), mammary gland tumors; 69 (2.8%), hematologic tumors; 39 (1.6%), cancer of unknown primary origin; 28 (1.1%), sarcomas; 16, skin tumors (0.7%); and 26 (1.1%), others. Figure 2 shows combination therapy with opi-

oids in this study. Morphine alone was administered to 969 patients (39.7%), while opioids including morphine were given to 1127 patients (46.1%). Opioid or opioids other than morphine were received by 347 patients (14.2%). Morphine-treated patients accounted for 85.8%. Figure 3 illustrates opioids and dosage forms having been administered up until death. Morphine alone was given to 1776 patients (81.0%); fentanyl, 289 (13.2%); oxycodone, 127 (5.8%). By dosage form, injection, adhesive patch, and suppository were used in 2128 patients (97.1%), 63 (2.9%), and 1 (0.05%), respectively.

Characteristics of Opioid Antagonist-Treated Patients Respiratory depression-responsible opioids were morphine and oxycodone in 6 (hydrochloride, 5; sulfate, 1) and 1, respectively, of the 7 patients treated with opioid antagonists. The characteristics of these patients were as follows: age, 74±5 years; height, 162±11 cm; body weight, 49.3±5.2 kg; BMI, 18.7±0.8 kg/m^2; and PPS, 20 (10–20). These 7 patients consisted of 4 with lung cancer, 1 with stomach cancer, 1 with pancreatic cancer, and 1 with rectal cancer. Factors affecting respiratory functions were pulmonary metastases (including intrapulmonary metastasis) in 4 patients, pleural effusion in 3, oxygen inhalation in 3, and ascites in 1. Dementia was found in 4 patients. Concomitant drugs included NSAIDs (3 patients), zoledronic acid (2), corticosteroids (3), antipsychotics (6), hypnotics (2), and antidepressant (1).

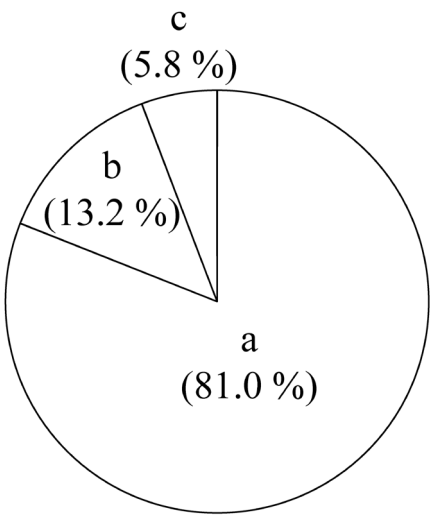

Fig. 3. Opioids and Dosage Forms Having Been Used until Death (n=2192)

a: Morphine, 1776 patients (morphine hydrochloride injection, 1775; morphine hydrochloride suppository, 1). b: Fentanyl, 289 patients (injection, 226; adhesive patch, 63). c: Oxycodone, 127 patients (injection, 127). Patients discharged or transferred to other hospitals were excluded.

Changes in Blood Test Results at the Onset of Respiratory Depression In morphine-treated patients, SCr was significantly (p=0.03) elevated from 1.37 (0.48–1.76) mg/dL the day before the start of morphine to 2.76 (1.60–3.88) mg/dL at the onset of respiratory depression. eGFR was also significantly (p=0.03) aggravated, from 35.8 (30.1–121) mL/min/1.73 m^2 the day before morphine start to 20.2 (12.3–48.9) mL/min/1.73 m^2 at the onset of respiratory depression. Between the day before the start of an opioid and the onset of respiratory depression, the oxycodone-treated patient showed SCr change from 1.29 to 1.06 mg/dL, and eGFR change from 42.2 mL/min/1.73 m^2 to 52.3 mL/min/1.73 m^2. In morphine-treated patients showed AST change from 33 (18.8–56.5) to 41 (23–97.5) IU/L (p=0.22); ALT also change from 18.5 (12.3–36.3) to 25.5 (10–36.8) IU/L (p=0.44). In the oxycodone-treated patient, AST and ALT were changed at 18 and 10 IU/L, respectively.

Changes in Administration Method of Opioids between before and after Opioid Antagonist Administration Table 1 shows changes in opioid administration method between before and after opioid antagonist administration. Opioids were most frequently used for dyspnea in 5 patients, who were all treated with morphine. Opioids were administered intravenously and by the enteral route in 6 patients and 1 patient, respectively. The median dosage of opioids, as converted to morphine injection, was 13.3 (10–30) mg/d. The onset of respiratory depression was observed at this dosage of opioids in 4 patients; and at patient-adjusted dosage and after route change in 3 patients. After opioid antagonist administration,

Table 1. Changes in Opioid Administration Method between before and after Opioid Antagonist Administration

Case	Tumor type	Before opioid antagonist administration					Opioid antagonist administration method		After opioid antagonist administration		
		Indication	Opioid	Route	Dosage (mg/d)	Dosing situation[a)]	Opioid antagonist[b)]	Dosing frequency	Opioid	Route	Dosage (mg/d)[c)]
1	Lung	Dyspnea Pain	Morphine sulfate	Enteral	40	Same dose continued	Levallorphan	2	Morphine hydrochloride	Venous	10
2	Lung	Dyspnea	Morphine hydrochloride	Venous	20	Same dose continued	Levallorphan	1	Fentanyl	Venous	0.1
3	Lung	Dyspnea	Morphine hydrochloride	Venous	10	1 d after switch from rescue to continuous dosing	Levallorphan	1	Fentanyl	Venous	0.3
4	Pancreas	Dyspnea	Morphine hydrochloride	Venous	30	2 d after 50% increase	Levallorphan	1	Fentanyl	Venous	0.3
5	Stomach	Pain	Morphine hydrochloride	Venous	10	Same dose continued	Levallorphan	1	Fentanyl	Venous	0.2
6	Rectum	Dyspnea Pain	Morphine hydrochloride	Venous	30	Same dose continued	Levallorphan	2	Fentanyl	Venous	0.8
7	Lung	Pain	Oxycodone	Venous	8	1 d after switch from oral to vein route	Naloxone	3	Fentanyl	Venous	0.1

a) Changes if any in opioid administration method before opioid antagonist administration. *b*) Opioid antagonist was switched from levallorphan to naloxone in June 2013 because of stock status in our hospital. *c*) As the conversion ratio for opioid, 3 : 1 was used for oral morphine to injectable morphine; 4 : 3, for oral oxycodone to injectable oxycodone; 40 : 50 : 1, for morphine injection, oxycodone injection, and fentanyl injection.

opioids were switched to fentanyl in 6 patients. In 1 patient, morphine was continued at a reduced dosage. The median survival time after opioid antagonist administration was 5 (3–10) d.

DISCUSSION

To our knowledge, this study is the first to collect cases in which opioid antagonists were administered against respiratory depression occurring in terminal cancer patients who had been treated with opioids at optimal dosage and to elucidate the detailed course of disease.

The most important aspect of this study is to have demonstrated that the proper use of opioids enables safe treatment in almost all patients. All of the 2443 patients who received opioids had poor systemic conditions, as indicated by baseline PPS 35 (30–40). The most common tumor type was respiratory tract tumor. Therefore, most of these patients were in the cancer terminal stages with prognoses of less than one month, and might have had reduced respiratory functions. In association with systemic debility attributable to cancer progression, terminal cancer patients may experience reduced respiratory and renal functions. Occasionally, renal impairment due to NSAIDs and/or zoledronic acid commonly used at the terminal stage of cancer may occur.[23,24] Among opioids, particularly morphine and morphine-6-glucuronide are likely to be used at overdoses, possibly leading to the onset of respiratory depression.[25] European Association for Palliative Care and European Society for Medical Oncology guidelines recommend fentanyl as the first choice in patients with glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m^2.[26,27] In this study, there was no case in which morphine was administered for eGFR <30 mL/min/1.73 m^2. Although 3 patients had an eGFR of nearly 30 mL/min/1.73 m^2, all of them received morphine owing to dyspnea. Since symptom mitigation with opioids other than morphine was difficult, morphine was used at as low doses as possible. At the terminal stages of cancer when blood tests are unlikely to be carried out, if the renal function suddenly declines, accurate estimation of GFR is difficult. In addition, terminal cancer patients are very likely to be accompanied by sarcopenia due to cancer cachexia.[28] Since SCr is also decreased with muscle mass decrease, evaluation of renal function requires careful attention to avoid overestimation. The doses of opioids may become overdoses not only at the start of administration or at the change of administration method, but also when the initial low doses are continued, as indicated in this study and as Iwase *et al.* also reported that even low doses of morphine can induce respiratory depression.[5] The present study reveals that the rate of patients who required treatment with opioid antagonists was 0.3% of terminal cancer patients who had been treated with opioids. This rate is near to the lowest level among patients requiring opioid antagonists (excluding cancer patients at the terminal stage), which has been reported as 0.2 to 0.9%.[12] Because the low incidence of respiratory depression in the current study can be explained by the fact that pharmacotherapy with opioids was administered appropriately in accordance with guidelines and a hospital manual.[16,26,27] Table 1 shows multiple doses of an opioid antagonist were required in cases 1, 6, and 7. In cases 1 and 7, despite low doses, the reason for multiple doses is owing to the finding that drug efficacy was prolonged by the enteral route of a sustained-release formulation and the oral route of a sustained-release formulation prior to switching to injection. In case 6, one reason is that a relatively high dose was required and the other reasons being that the opioid antagonist used was levallorphan, not a complete antagonist, unlike naloxone.[17,18] In cases 2–5, a single dose of an opioid antagonist improved respiratory depression, possibly because opioids had been administered only by injection. These findings indicate that switching from opioid sustained release formulation to opioid injection at the cancer terminal stages can be safely carried out at reduced doses rather than at equivalent analgesic doses in consideration of patient's systemic conditions and pre-switching pharmacokinetics.[29] Parameters affecting respiratory function might have indicated respiratory dysfunction due to complications related to the respiratory system. As for other drugs than opioids, corticosteroids were used concomitantly in 3 cases. Corticosteroids may induce sarcopenia due to myopathy, especially respiratory muscle decline.[30] Therefore they should not be used for a long-term duration in terminal cancer patients.[31] Concomitant use of antipsychotic, hypnotic, or antidepressant drugs may enhance central nervous system depressant effect and affect the respiratory function. Nevertheless, the current study demonstrated that opioid antagonists ameliorated respiratory depression in all cases, implying lesser effect of concomitant drugs on respiratory function.

The second important issue in this study is that oral administration of opioids becomes difficult in terminal cancer patients. Of the opioids having been used until the time of death, 81.0% was morphine and 97.1% was an injectable form. The reasons why morphine accounted for the major part may include that morphine is effective not only for pain relief but also for dyspnea mitigation and useful for terminal cancer patients because of availability at low cost and a variety of dosage forms.[32] Another reason is that oxycodone injection was added to opioids in Japan since 2012. For terminal cancer patients who experienced uncontrollable pain and who had difficulty in taking drugs orally, the subcutaneous or intravenous route is preferable for rapid analgesic effects.[26,27] In this study, 4 patients were comorbid with dementia. Observing signs of opioid overdose is difficult for these patients themselves. Even though dose reduction, dose suspension, or opioid switching is required, the injection form may be chosen and enforced. In general, opioids have no ceiling effect so that the upper limit of the dose is not yet established.[33] The amount of opioids used in Japan, although having increased in recent years, is still lower than the international standard, as reported, and has not reached the proper amount of use.[34] As the amount of use is estimated to increase toward the proper use, more attention should be paid to the administration of opioid overdose.

These results indicate that respiratory depression induced by opioid overdose should be avoided in the terminal stages of cancers by monitoring the patient's systemic condition, life prognosis, vital signs (especially, respiratory rate), somnolence, percutaneous arterial oxygen saturation, miosis, renal function, urine volume, and urine specific gravity as well as opioid type, dose, administration route, pharmacokinetics, drug efficacy, and concomitant drugs. Through monitoring of these parameters, a further decrease in the rate of need for opioid antagonists by terminal cancer patients can be accom-

plished. In the present study, a pharmacist found respiratory depression signs during patient rounding and administered opioid antagonists. Participation and collaboration in drug efficacy evaluation by not only physicians and nurses, but also pharmacists who have specialized knowledge of pharmacotherapy monitoring is considered to be useful for the proper use of opioids.[35)]

An interesting outcome of this study is the short survival time after opioid antagonist administration, of which the median value was 5 (3–10) d. Based on this study and a study by Kim *et al.* about the survival time of terminal cancer patients with dyspnea, it is suggested that life prognosis with dyspnea is shorter than expected in terminal cancer patients.[36)] Patients who received opioid antagonists in this study had PPS of 20 (10–20) before the onset of respiratory depression. This suggests that they may have been in the near-death period in which pathological conditions have been exacerbated, as compared with the day before the start of opioid administration, and were developing organopathy. Reduced respiratory and renal functions may have caused relative opioid overdose, resulting in the onset of respiratory depression. In the terminal stages of cancers, especially in the near-death stage, pharmacotherapy according to the time-course changes in pathological conditions is of importance. Furthermore, administration of opioid antagonists that may cause withdrawal syndrome must be carefully conducted in consideration of patient's pre-respiratory depression systemic conditions, life expectancy, and the minds of the patient and his/her family.[37)] The absence of withdrawal syndrome after opioid antagonist administration in this study may be attributed to patient-matched treatments including opioid antagonist administration, opioid switching, and continued opioid administration at reduced doses.

This study has the following limitations: first, respiratory depression induced by opioid overdose is difficult to predict and the study population is small enough to require a long duration to reach the big sample size, leading to a single-site retrospective study. Accordingly, these situations must be considered in data interpretation. Nevertheless, this study characterized by involving terminal cancer patients alone is worth while doing. Second, blood opioid concentrations were not measured and a diagnosis of opioid-induced respiratory depression was made on the basis of clinical symptoms. In these patients, respiratory depression was judged as an adverse event of opioids because respiratory depression was improved by opioid antagonist administration.

Ultimately, the proper use of opioids was safe in almost all terminal cancer patients of this study. Regarding morphine, however, a rare event was observed: first, there were respiratory and renal dysfunctions associated with systemic debility due to progression of disease, followed by renal impairment caused by NSAIDs or zoledronic acid, both commonly used in the terminal stages of cancer; then, morphine given at optimal doses and a metabolite morphine-6-glucuronide became relatively excessive, leading to the onset of respiratory depression. This highlights the importance of pharmacotherapy monitoring for sudden pathological changes in the terminal stages of cancer.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

1) Ministry of Health, Labour and Welfare. "Overview of the 2013 Demographic Statistics Monthly year meter (approximate).": ‹http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai13/dl/gaikyou25.pdf›, cited 19 June, 2015.
2) Morita T, Tsunoda J, Inoue S, Chihara S. Contributing factors to physical symptoms in terminally-ill cancer patients. *J. Pain Symptom Manage.*, **18**, 338–346 (1999).
3) Qaseem A, Snow V, Shekelle P, Casey DE Jr, Cross JT Jr, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of Physicians, Dallas P, Dolan NC, Forciea MA, Halasyamani L, Hopkins RH Jr, Shekelle P. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann. Intern. Med.*, **148**, 141–146 (2008).
4) Japanese Society for Palliative Medicine. *Clinical guidelines for Cancer Pain Management Second Edition*. Kanehara & Co., LTD., Tokyo, pp. 60–63 (2014).
5) Iwase S, Murakami T, Umenai M, Saitou Y, Nakagawa K. Morphine metabolite activity—Report on pancreatic cancer patient under terminal care that developed respiratory depression with a low dose of morphine-. *Rinsho Iyaku*, **20**, 977–981 (2004).
6) Sweeney C, Bogan C. *Textbook of Palliative Medicine*. Hodder Arnold, London, pp. 390–401 (2006).
7) Southern DA, Read MS. Overdosage of opiate from patient controlled analgesia devices. *BMJ*, **309**, 1002 (1994).
8) Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL. Side effects of opioids during short-term administration: effect of age, gender, and race. *Clin. Pharmacol. Ther.*, **74**, 102–112 (2003).
9) Ostermeier AM, Roizen MF, Hautkappe M, Klock PA, Klafta JM. Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. *Anesth. Analg.*, **85**, 452–460 (1997).
10) Taylor S, Kirton OC, Staff I, Kozol RA. Postoperative day one: a high risk period for respiratory events. *Am. J. Surg.*, **190**, 752–756 (2005).
11) Flisberg P, Rudin A, Linnér R, Lundberg CJ. Pain relief and safety after major surgery. A prospective study of epidural and intravenous analgesia in 2696 patients. *Acta Anaesthesiol. Scand.*, **47**, 457–465 (2003).
12) Baxter AD. Respiratory depression with patient-controlled analgesia. *Can. J. Anaesth.*, **41**, 87–90 (1994).
13) Izumi N, Okuyama S, Abe K, Ishikawa D, Suzuki S. Prolonged disturbance of consciousness and respiratory depression induced by controlled-release morphine, requiring long-term naloxone administration in a hemodialysis patient with cancer—a case report. *Gan To Kagaku Ryoho*, **39**, 1295–1299 (2012).
14) Pauli-Magnus C, Hofmann U, Mikus G, Kuhlmann U, Mettang T. Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. *Nephrol. Dial. Transplant.*, **14**, 903–909 (1999).
15) Fallon M, Cherny NI, Hanks G. *Oxford Textbook of Palliative Medicine Fourth Edition*. Oxford University Press, New York, pp. 661–671 (2010).
16) National Comprehensive Cancer Network (Version 2.2013). *NCCN Clinical Practice Guidelines in Oncology* (*NCCN Guidelines®*). *Adult Cancer Pain*.
17) Package insert of Naloxone hydrochloride intravenous injection 0.2 mg "DAIICHI SANKYO," revised 10th ed, by Alfresa Pharma Corporation, Osaka (October 2011).
18) Package insert of Lorfan injection 1 mg, revised 7th ed, by Takeda Pharmaceutical Company Limited, Tokyo (July 2011).
19) Chan KS, Tse DMW, Sham MMK, Thorsen AB. *Oxford Textbook*

of Palliative Medicine Fourth Edition. Oxford University Press, New York, pp. 1107–1113 (2010).
20) Higashiguchi T, Ikegaki J, Sobue K, Tamura Y, Nakajima N, Futamura A, Miyashita M, Mori N, Inui A, Ohta K, Hosokawa T. Guidelines for parenteral fluid management for terminal cancer patients. *Jpn. J. Clin. Oncol.*, **46**, 986–992 (2016).
21) Anderson F, Downing GM, Hill J, Casorso L, Lerch N. Palliative performance scale (PPS): a new tool. *J. Palliat. Care*, **12**, 5–11 (1996).
22) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am. J. Kidney Dis.*, **53**, 982–992 (2009).
23) Schneider V, Lévesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. *Am. J. Epidemiol.*, **164**, 881–889 (2006).
24) Tassinari D, Poggi B, Nicoletti S, Fantini M, Tamburini E, Possenti C, Sartori S. Zoledronic acid treatment at home: safety data from an observational prospective trial. *J. Palliat. Med.*, **10**, 352–358 (2007).
25) Osborne RJ, Joel SP, Slevin ML. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br. Med. J.* (Clin. Res. Ed.), **292**, 1548–1549 (1986).
26) Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, Fallon M, Hanna M, Haugen DF, Juhl G, King S, Klepstad P, Laugsand EA, Maltoni M, Mercadante S, Nabal M, Pigni A, Radbruch L, Reid C, Sjogren P, Stone PC, Tassinari D, Zeppetella G, European Palliative Care Research Collaborative (EPCRC), European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol.*, **13**, e58–e68 (2012).
27) Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F; ESMO Guidelines Working Group. Management of cancer pain: ESMO Clinical Practice Guidelines. *Ann. Oncol.*, **23** (Suppl. 7), vii139–vii154 (2012).
28) Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.*, **12**, 489–495 (2011).
29) Fine PG, Portenoy RK, *Ad hoc* expert panel on evidence review and guidelines for opioid rotation. Establishing "best practices" for opioid rotation: conclusions of an expert panel. *J. Pain Symptom Manage.*, **38**, 418–425 (2009).
30) van Balkom RH, van der Heijden HF, van Herwaarden CL, Dekhuijzen PN. Corticosteroid-induced myopathy of the respiratory muscles. *Neth. J. Med.*, **45**, 114–122 (1994).
31) Paulsen O, Klepstad P, Rosland JH, Aass N, Albert E, Fayers P, Kaasa S. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J. Clin. Oncol.*, **32**, 3221–3228 (2014).
32) Mazzocato C, Buclin T, Rapin CH. The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: a randomized double-blind controlled trial. *Ann. Oncol.*, **10**, 1511–1514 (1999).
33) World Health Organization. *Cancer pain relief*, 2nd edition. World Health Organization, Geneva (1996).
34) Duthey B, Scholten W. Adequacy of opioid analgesic consumption at country, global, and regional levels in 2010, its relationship with development level, and changes compared with 2006. *J. Pain Symptom Manage.*, **47**, 283–297 (2014).
35) Uekuzu Y, Higashiguchi T, Futamura A, Ito A, Ohara H, Tsuzuki N, Nakagawa A, Ito T, Mogami K, Asai H, Kikukawa E. Efficacy of multidisciplinary opioid injection preparation system. *Jpn. J. Pharm. Health Care Sci.*, **40**, 237–244 (2014).
36) Kim YH, Okuda C, Sakamori Y, Masago K, Togashi Y, Mishima M. Continuous morphine infusion for end-stage lung cancer patients. *Oncol. Lett.*, **5**, 972–974 (2013).
37) Manfredi PL, Ribeiro S, Chandler SW, Payne R. Inappropriate use of naloxone in cancer patients with pain. *J. Pain Symptom Manage.*, **11**, 131–134 (1996).