

Opioids have no negative effect on the survival time of patients with advanced lung cancer in an acute care hospital

Seigo Minami · Kosuke Fujimoto · Yoshitaka Ogata · Suguru Yamamoto · Kiyoshi Komuta

Received: 8 September 2014 / Accepted: 21 December 2014 / Published online: 7 January 2015
© Springer-Verlag Berlin Heidelberg 2015

Abstract

Purpose The purpose of this study is to determine whether or not opioid administration influenced the survival time of patients with advanced lung cancer in an acute care hospital setting.

Methods This was a single institutional and retrospective study. We reviewed patients with advanced lung cancer who had died from January 2008 to December 2013 at the Osaka Police Hospital. We compared survival times, calculated from the time of the last hospitalization or the last chemotherapy, between patients who had not used any opioids, those who had used a low dose of opioids (<60 mg/day), and those who had used a higher dose of opioids (≥60 mg/day).

Results A total of 369 patients, of which 284 had received chemotherapy, were analyzed. Opioid users were generally younger than nonusers. There was no significant difference in survival time after the last hospitalization in terms of opioid dose at the last admission and mean daily opioid dose; there was also no significant difference in survival time after the last chemotherapy in terms of the mean daily opioid dose and the opioid dose at death. Univariate and multivariate Cox

proportional hazard analysis regarding survival time after the last hospitalization or the last chemotherapy did not reveal any opioid-related variables as a significant predictive factor.

Conclusions Opioids were found to have no negative influence on survival time even in an acute care hospital.

Keywords Opioid · Lung cancer · Survival · Last hospitalization · Last chemotherapy

Introduction

Opioids are indispensable in cancer-related symptom management. However, many cancer patients [1, 2] and the general population [3] have a variety of concerns regarding opioid therapy, including fear of shortened survival time.

A randomized placebo-controlled study of opioids for patients with cancer symptoms would not be ethically approved. Some retrospective cohort studies have tried to demonstrate that opioids had no negative effects on the survival time of terminally ill cancer patients [4–10]. In an Israeli study involving hospice inpatients treated with morphine, no significant difference was observed regarding survival time in the hospice setting both between two dose groups (<300 vs. ≥300 mg/day; mean survival time of 14 vs. 15 days) and among three dose groups (<300 vs. 300–599 vs. ≥600 mg/day) according to the mean daily oral morphine equivalent dose (OMED) [7]. In a Japanese study involving hospice inpatients, there was no significant difference in survival time in the hospice setting among three groups according to the use of opioids within the final 48 h (OMED <240 mg/48 h vs. 240–599 mg/48 h vs. ≥600 mg/48 h) [8]. In contrast, other studies have suggested that a higher dose of opioids can potentially achieve longer survival in terminal patients. In another Israeli study,

Seigo Minami and Kosuke Fujimoto contributed equally to this study.

Electronic supplementary material The online version of this article (doi:10.1007/s00520-014-2592-6) contains supplementary material, which is available to authorized users.

S. Minami (✉) · K. Fujimoto · Y. Ogata · S. Yamamoto · K. Komuta

Department of Respiratory Medicine, Osaka Police Hospital,
10-31 Kitayama-cho, Tennoji-ku, Osaka-City, Osaka 543-0035,
Japan
e-mail: seigominami@oph.gr.jp

Present Address:

K. Fujimoto
Osaka University Graduate School of Medicine, Internal Medicine,
Allergy and Rheumatic Diseases, 2-2 Yamada-oka, Suita,
Osaka 565-0871, Japan

outpatients in a home care hospice setting treated with a high (300–599 mg/day; mean survival time of 87 days) and a very high (≥ 600 mg/day; mean survival time of 50 days) mean daily dose of OMED survived significantly longer than those treated with low (≤ 59 mg/day; mean survival time of 37 days) and moderate (60–299 mg/day; mean survival time of 36 days) doses [5]. A study involving 13 hospice programs in the USA also showed that the hospice stay was significantly longer for patients who received an intravenous morphine equivalent (IVME) dose >200 mg/day than for those who received an IVME dose ≤ 200 mg/day (≤ 200 vs. >200 mg/day; mean hospice stay of 28 vs. 47 days) [9]. The previous studies investigated inpatients in a hospice setting [4, 6–10] or outpatients under treatment by an home care hospice service [5] provided by palliative care experts. No study has surveyed cancer patients in an acute care hospital setting.

In our study, we retrospectively compared two end-of-life survival parameters, namely time of survival after the last hospitalization or after the last chemotherapy. The ultimate aim of our study was to determine whether or not opioid administration influenced survival time in patients with advanced lung cancer in an acute care hospital setting.

Materials and methods

Patient selection and experimental design

The study was carried out at the Osaka Police Hospital, a 580-bed private teaching and acute care hospital. Osaka Police Hospital had neither a palliative care unit/hospice nor a board-certified specialist from the Japanese Society for Palliative Medicine. We retrospectively reviewed the medical records and collected data on patients who had died of advanced lung cancer from January 2008 to December 2013 at Osaka Police Hospital and had been followed up continuously since the last chemotherapy or last admission until death. The data collected from all of the patient medical records included the following: sex; age at death; histological type; European Clinical Oncology Group (ECOG) performance status (PS), brain and bone metastases at the last chemotherapy and the last admission; a history of radiotherapy including whole brain irradiation and γ -knife therapy, systemic chemotherapy, endotracheal intubation, mechanical ventilation including noninvasive positive pressure ventilation, and any cardiopulmonary resuscitation (CPR) treatment; duration of the last hospitalization period; and survival time after the last chemotherapy. Screening of brain and bone metastases was not mandatory at the last chemotherapy and the last admission. CPR in our hospital involved the performance of either or both chest compressions and endotracheal intubation in the case of cardiopulmonary arrest. The data on opioid users included the following three opioid doses. (1) A daily regular opioid dose was the

sum of the fixed scheduled dose without rescue use within a day before the last admission or the last chemotherapy, because we did not have data regarding the precise use of rescue opioids especially in outpatients. (2) The opioid dose at death was the total daily dose estimated from the rate of opioid infusion at the time of death for patients who underwent intravenous or subcutaneous administration or was the fixed scheduled dose without rescue use at the time of death for patients who underwent oral administration. This was because we were unable to obtain the precise cumulative dose that was actually used within 24 h before death from our medical records. Some patients had received a rapidly increased opioid dosage as death approached. Other patients died so quickly after the last admission that we failed to obtain the data regarding the rescue dose before admission. (3) For the mean daily opioid dose, the cumulative prescribed opioid dose was divided by the number of days when any opioids were regularly administered. Patients were treated using different opioids, and for all analyses, opioid doses were converted to an OMED according to Table 1. These doses were arbitrarily defined because conversion rates varied between some of the guidelines and conversion tables. Neither pentazocine nor buprenorphine was used for cancer-related symptom management during the study period. Pentazocine is administered intramuscularly as routine premedication for bronchoscopy, but its use was negligible in this study because few patients experienced bronchoscopy during the end-of-life evaluation period. We neglected codeine in this study because we could not establish precise codeine usage but considered that total doses used had been very small. Only cough medicine containing 1 % codeine phosphate and dihydrocodeine phosphate is commercially available in Japan. Neither undiluted codeine nor other opioids were available in our hospital during the study period. The Osaka Police Hospital ethics committee

Table 1 Conversion rates for various opioids into the oral morphine equivalent dose

Opioids	Equivalent dose
Morphine	
Oral	60 mg/day
Suppository	40 mg/day
Intravenous/Subcutaneous	30 mg/day
Oxycodone	
Oral	40 mg/day
Intravenous	30 mg/day
Fentanyl	
Transdermal patch release rate	25 μ g/h
Intravenous/Subcutaneous	0.6 mg/day
Tramadol	
Oral	300 mg/day

approved this study and waived the requirement for informed consent.

Data analysis

The data for normally distributed continuous variables, discrete variables, and categorical variables were expressed as the mean $\pm$ standard deviation (SD), median (range), and frequency.

To assess the survival times, we defined two parameters: (1) the number of days from the admission day of the last hospitalization until death, namely the last hospitalization period, and (2) the number of days from the last chemotherapy until death, namely the survival time after the last chemotherapy. Regarding the latter parameter, the first day of the measured survival time was not the day when we determined discontinuation of chemotherapy, because decisions regarding the withdrawal of chemotherapy were sometimes ambiguous; however, it was the day when the last antitumor drugs were administered either orally or intravenously. To investigate the influence of opioid dose on survival, we arbitrarily divided our patients into three groups and compared them with each other: opioid nonusers, users who received a low dose of opioid (<60 mg/day), and users who received a high dose of opioids (≥ 60 mg/day). For this division, we referred to a previous study by Bercovitch et al. showing that high morphine dosage did not affect patient survival. In this study, 60 mg/day was defined as the cutoff dose between low and moderate daily regular morphine dosages [5]. Considering the actual opioid dose of our patients, a higher cutoff value would have resulted in a more imbalanced grouping in terms of patient number.

First, to explore the effect of opioid use on survival, the survival curves were compared between the three groups. The survival curves were plotted using the Kaplan-Meier method, and comparisons were based on the log-rank test. When a significant difference was found, the Bonferroni correction was adopted to compare each of the two groups.

Second, to examine how opioids influenced survival, the following five variables were added as an independent variable in the Cox proportional hazard regression model: four background variables, namely ECOG PS, sex, age at death, and bone metastasis, and one of the following three opioid-related variables, namely opioid dose at the last admission or the last chemotherapy, mean daily opioid dose during the last hospitalization or after the last chemotherapy, and opioid dose at death. The results were evaluated in terms of the risk ratio (RR) and 95 % confidence interval (CI).

A p value <0.05 was considered as being statistically significant. Contingency table methods in combination with chi-square or G-tests for relative frequencies and one-way analysis of variance with the Tukey post hoc test for normally distributed continuous variables were used to evaluate the

baseline differences between the three groups. All statistical analyses were performed using StatMate statistical software (StatMate version IV: ATMS Co., Ltd., Tokyo, Japan).

Results

Between January 2008 and December 2013, 369 patients died at Osaka Police Hospital. Among the 285 patients who had received chemotherapy, one patient was excluded because he had received chemotherapy at another hospital and the precise date was unknown. Patient baseline characteristics are detailed in Supplemental Table 1.

First, we divided the 369 dead patients into three groups based on opioid dose at the last admission, the mean daily opioid dose during the last hospitalization, and the opioid dose at death. Patient baseline characteristics and opioid usage are shown in Tables 2, 3, and 4 and Supplemental Table 2. Opioid users were younger and more frequently had bone metastasis at the last admission than opioid nonusers (Tables 2, 3, and 4). Opioid users according to mean daily opioid dose during the last hospitalization died more frequently in general wards and received endotracheal intubation and CPR treatment less often during the last hospitalization than opioid nonusers (Table 3). Opioid users treated with doses of ≥ 60 mg/day at death more frequently received mechanical ventilation during the last hospitalization than opioid nonusers and users treated with a lower dose at death (Table 4). Although various opioids were used during the last hospitalization, extended-release oxycodone and the transdermal fentanyl patch were the most frequently used opioids at the last admission for patients with an OMED <60 mg/day (68 %) and for those who had received an OMED ≥ 60 mg/day (80 %), respectively (Supplemental Table 2). On the other hand, intravenous morphine was the most frequently used opioid at death in both the lower-dose and higher-dose opioid user groups (77 and 80 %, respectively) (Supplemental Table 2). Figure 1 shows the survival curves after the last admission. No significant difference in the duration of the last hospitalization periods was observed between the three groups, when evaluated in terms of opioid dose at the last admission and the mean daily opioid dose during the last hospitalization (Fig. 1a, b). However, opioid nonusers survived significantly longer since the commencement of their last hospitalization than opioid users with an OMED at death of 60 mg/day (opioid nonusers vs. users <60 mg/day; median survival time of 24 vs. 17 days; log-rank $p < 0.01$; Fig. 1c).

Second, we divided the 284 patients who had received chemotherapy into three groups in terms of opioid dose at the last chemotherapy, mean daily opioid dose after the last chemotherapy, and opioid dose at death. Supplemental Tables 3, 4, 5, and 6 detail patient baseline characteristics and opioid usage. Opioid users were younger and more

Table 2 Patient backgrounds in the three groups at the last hospitalization period compared in terms of opioid dose at the last admission ($N=369$)

	No opioid	<60 mg/day	≥60 mg/day	<i>p</i> value
<i>N</i>	231	88	50	
Age at death (years)				
Mean±SD	72.0±9.2	68.4±10.5	68.4±10.5	<0.01 ^a
		No opioid vs. <60 mg/day		<0.01 ^b
		No opioid vs. ≥60 mg/day		<0.05 ^b
		<60 vs. ≥60 mg/day		NS ^b
Sex				
Male/Female	172/59	61/27	38/12	0.59 ^c
ECOG PS at admission				
0–1/2/3/4	12/42/88/89	4/13/41/30	0/9/23/18	
		PS 0–2 vs. PS 3–4		0.58 ^c
Distant metastases at admission				
Brain				
Yes/no or not examined	76/155	35/53	16/34	0.48 ^c
Bone				
Yes/no or not examined	40/191	35/53	28/22	<0.001 ^c
		No opioid vs. <60 mg/day		<0.001 ^d
		No opioid vs. ≥60 mg/day		<0.001 ^d
		<60 vs. ≥60 mg/day		0.20 ^d
Place of admission				
General ward/ICU, HCU/ER	211/18 /2	85/0/3	47/3/0	
		General ward vs. others		0.22 ^e
Place of death				
General ward/ICU, HCU/ER	228/1/2	85/0/3	50/0/0	
		General ward vs. others		0.26 ^e
Treatment during last hospitalization				
Chemotherapy				
Yes/No	43/188	14/74	9/41	0.85 ^c
Radiotherapy				
Yes/No	19/212	8/80	4/46	0.96 ^c
Endotracheal intubation				
Yes/No	8/223	1/87	0/50	0.15 ^e
Mechanical ventilation				
Yes/No	11/220	2/86	2/48	0.59 ^e
CPR treatment				
Yes/No	11/220	4/84	2/48	0.97 ^e

CPR cardiopulmonary resuscitation, ECOG PS Eastern Cooperative Oncology Group performance status, ER emergency room, HCU high care unit, ICU intensive care unit, NS not significant, SD standard deviation

^a Analysis of variance (ANOVA)

^b Tukey method

^c χ^2 test

^d χ^2 test with Bonferroni correction

^e G-test

frequently had bone metastasis at the last chemotherapy than opioid nonusers (Supplemental Tables 3, 4, and 5), while

opioid users treated with a low dose of <60 mg/day most frequently had brain metastasis at the last chemotherapy

Table 3 Patient background in the three groups at the last hospitalization period compared in terms of mean daily opioid dose during the last hospitalization ($N=369$)

	No opioid	<60 mg/day	≥60 mg/day	<i>p</i> value
<i>N</i>	81	187	101	
Age at death (years)				
Mean±SD	72.3±10.0	71.3±9.0	68.0±9.5	<0.01 ^a
		No opioid vs. <60 mg/day		NS ^b
		No opioid vs. ≥60 mg/day		<0.01 ^b
		<60 vs. ≥60 mg/day		<0.05 ^b
Sex				
Male/Female	64/17	128/59	79/22	0.09 ^c
ECOG PS at admission				
0–1/2/3/4	5/12/22/42	7/37/83/60	4/15/47/35	0.64 ^c
Distant metastases at admission				
Brain				
Yes/no or not examined	31/50	58/129	38/63	0.38 ^c
Bone				
Yes/no or not examined	10/71	53/134	49/61	<0.001 ^c
		No opioid vs. <60 mg/day		0.01 ^d
		No opioid vs. ≥60 mg/day		<0.001 ^d
		<60 mg/day vs. ≥60 mg/day		0.01 ^d
Place of admission				
General ward/ICU, HCU/ER	71/6/4	179/7/1	93/8/0	0.06 ^c
		General ward vs. others		
Place of death				
General ward/ICU, HCU/ER	76/1/4	186/0/1	101/0/0	0.03 ^e
		General ward vs. others		0.04 ^f
		No opioid vs. <60 mg/day		0.11 ^f
		No opioid vs. ≥60 mg/day		0.75 ^e
		<60 vs. ≥60 mg/day		
Treatment during last hospitalization				
Chemotherapy				
Yes/No	11/70	40/147	15/86	0.20 ^e
Radiotherapy				
Yes/No	8/73	15/172	9/92	0.88 ^c

Table 3 (continued)

	No opioid	<60 mg/day	≥60 mg/day	<i>p</i> value
Endotracheal intubation				
Yes/No	7/74	0/187	2/99	<0.001 ^e <0.001 ^f 0.26 ^f 0.71 ^f
		No opioid vs. <60 mg/day No opioid vs. ≥60 mg/day <60 vs. ≥60 mg/day		
Mechanical ventilation				
Yes/No	3/78	6/181	6/95	0.56 ^e
CPR treatment				
Yes/No	10/71	3/184	4/97	<0.01 ^e 0.002 ^f 0.20 ^f 0.40 ^e
		No opioid vs. <60 mg/day No opioid vs. ≥60 mg/day <60 vs. ≥60 mg/day		

CPR cardiopulmonary resuscitation, ECOG PS Eastern Cooperative Oncology Group performance status, ER emergency room, HCU high care unit, ICU intensive care unit, NS not significant, SD standard deviation

^a Analysis of variance (ANOVA)

^b Tukey method

^c χ^2 test

^d χ^2 test with Bonferroni correction

^e G-test

^f G-test with Bonferroni correction

Table 4 Patient backgrounds in the three groups at the last hospitalization period compared in terms of opioid dose at death ($N=369$)

	No opioid	<60 mg/day	≥60 mg/day	<i>p</i> value
<i>N</i>	78	139	152	
Age at death (years)				
Mean±SD	73.7±9.0	70.7±9.2	69.1±9.7	<0.01 ^a
		No opioid vs. <60 mg/day		NS ^b
		No opioid vs. ≥60 mg/day		<0.01 ^b
		<60 vs. ≥60 mg/day		NS ^b
Sex				
Male/Female	60/18	100/39	111/41	0.72 ^c
ECOG PS at admission				
0–1/2/3/4	5/14/22/37	4/ 21/65/49	7/29/65/51	
		PS 0–2 vs. PS 3–4		0.41 ^c
Distant metastases at admission				
Brain				
Yes/no or not examined	31/47	46/93	50/102	0.54 ^c
Bone				
Yes/no or not examined	11/67	34/105	58/94	<0.001 ^c
		No opioid vs. <60 mg/day		0.21 ^d
		No opioid vs. ≥60 mg/day		<0.001 ^d
		<60 vs. ≥60 mg/day		0.04 ^d
Place of admission				
General ward/ICU, HCU/ER				
	70/6/2	130/7/2	143/8/1	0.45 ^c
Place of death				
General ward/ICU, HCU/ER				
	75/1/2	137/0/2	151/0/1	0.27 ^c
Treatment during last hospitalization				
Chemotherapy				
Yes/No	16/62	20/119	30/122	0.39 ^c
Radiotherapy				
Yes/No	9/69	6/133	17/135	0.07 ^c
Endotracheal intubation				
Yes/No	1/77	3/138	5/147	0.63 ^e
Mechanical ventilation				
Yes/No	0/78	1/138	14/138	<0.001 ^c
		No opioid vs. <60 mg/day		0.77 ^e
		No opioid vs. ≥60 mg/day		0.04 ^f
		<60 vs. ≥60 mg/day		0.008 ^f
CPR treatment				
Yes/No	2/76	5/134	10/142	0.31 ^e

CPR cardiopulmonary resuscitation, ECOG PS Eastern Cooperative Oncology Group performance status, ER emergency room, HCU high care unit, ICU intensive care unit, NS not significant, SD standard deviation

^a Analysis of variance (ANOVA)

^b Tukey method

^c χ^2 test

^d χ^2 test with Bonferroni correction

^e G-test

^f G-test with Bonferroni correction

(Supplemental Table 3). Opioid nonusers more frequently received endotracheal intubation and CPR treatment after the last chemotherapy than opioid users, according to mean daily opioid dose after the last chemotherapy and opioid dose at death (Supplemental Tables 4 and 5). Various opioids were administered after the last chemotherapy (Supplemental Table 6). Extended-release oxycodone and the transdermal fentanyl patch were the most frequently used opioids at the last chemotherapy in patients who received an OMED <60 mg/day (73 %) and those who received an OMED $\geq$ 60 mg/day (78 %), respectively. In contrast, intravenous morphine was the commonest opioid administered at death in both opioid user groups (76 and 78 %, respectively). The survival curves for patients after the last chemotherapy are plotted in Supplemental Fig. 1. No significant difference was observed in survival time after the last chemotherapy between the three groups in terms of mean daily opioid dose after the last chemotherapy and the opioid dose received at death

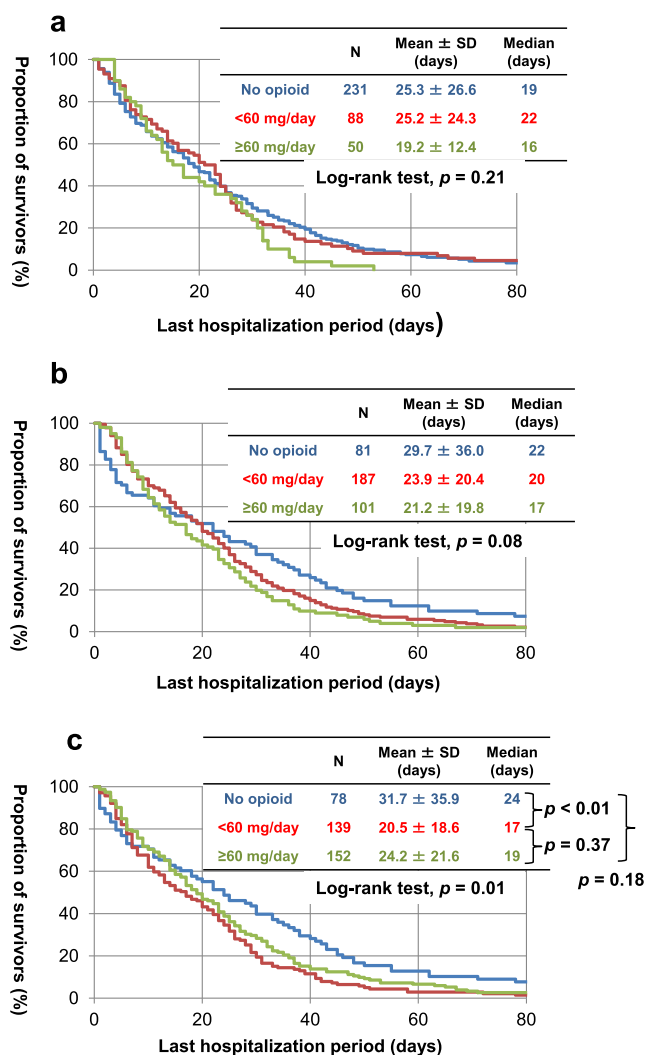


Fig. 1 The survival curves after the last admission: **a** opioid dose at the last chemotherapy, **b** mean daily opioid dose after the last chemotherapy, and **c** opioid dose at death

(Supplemental Fig. 1b, c). However, the survival time of opioid nonusers measured from the time of the last chemotherapy was significantly longer than that of opioid users with an OMED at the last chemotherapy of 60 mg/day (opioid nonusers vs. users of <60 mg/day: median survival time of 49.5 vs. 38.5 days; log-rank $p < 0.01$; Supplemental Fig. 1a).

Third, we performed univariate and multivariate Cox proportional hazard analysis regarding the relationship between the six independent variables and the dependent variables for survival time. The analysis of the last hospitalization period identified the ECOG PS at the last admission as an effective predictor of survival (univariate analysis [RR, 1.42; 95 % CI, 1.26–1.60; $p < 0.001$] and multivariate analysis [RR, 1.42; 95 % CI, 1.26–1.60; $p < 0.001$]); however, the analysis did not reveal any opioid-related variables as significant predictors of survival time (Table 5). On the other hand, the analyses regarding survival time after the last chemotherapy also showed that the ECOG PS at the last chemotherapy (univariate analysis [RR, 1.34; 95 % CI, 1.19–1.51; $p < 0.001$] and multivariate analysis [RR, 1.33; 95 % CI, 1.18–1.50; $p < 0.001$, representing the mean opioid dose after last chemotherapy]), age at death (univariate analysis [RR, 0.98; 95 % CI, 0.97–1.00; $p = 0.008$ and multivariate analysis [RR, 0.98; 95 % CI, 0.97–1.00; $p = 0.03$, representing the mean opioid dose]), and bone metastasis at the last chemotherapy (univariate analysis [RR, 1.43; 95 % CI, 1.11–1.85; $p = 0.007$ and multivariate analysis [RR, 1.52; 95 % CI, 1.16–1.98; $p = 0.002$, representing the mean opioid dose]) were statistically significant, but none of the opioid-related variables was clinically important as predictors of survival time (Supplemental Table 7).

Discussion

The present study is the first to evaluate the relationship between opioid use and survival time in an acute care hospital setting.

The most important finding was that opioid use had no negative influence on survival time. This conclusion was reached on the basis of the following two findings. (1) Survival times measured after the last admission to hospital or after the last chemotherapy were similar between opioid nonusers, opioid users with an OMED <60 mg/day, and those with an OMED $\geq$ 60 mg/day (Fig. 1a, b and Supplemental Fig. 1b, c). (2) Univariate and multivariate analyses revealed that the opioid dose did not affect the survival time (Table 5 and Supplemental Table 7). Regarding the former finding, there were the following two contrary findings in this study. (i) Opioid nonusing patients survived significantly longer after the last hospital admission than patients evaluated in terms of the opioid dose at the time of death (Fig. 1c). (ii) Opioid nonusers also survived significantly longer after the last chemotherapy than opioid users evaluated in terms of the opioid

Table 5 Univariate and multivariate Cox proportional hazard analysis of the relationship between variables and the last hospitalization period ($N=369$)

Risk factors	RR	95 % CI	<i>p</i> value						
(A) Univariate analyses									
ECOG PS at last admission	1.42	1.26–1.60	<0.001						
Sex ^a	0.82	0.65–1.03	0.09						
Age at death	1.00	0.99–1.01	0.79						
Bone metastasis at last admission ^b	1.04	0.84–1.29	0.72						
Opioid dose at last admission	1.00	1.00–1.00	0.20						
Mean opioid dose during last hospitalization	1.00	1.00–1.00	0.37						
Opioid dose at death	1.00	1.00–1.00	0.75						
(B) Multivariate analyses									
	Opioid dose at last admission			Mean opioid dose during last hospitalization			Opioid dose at death		
Risk factors	RR	95 % CI	<i>p</i> value	RR	95 % CI	<i>p</i> value	RR	95 % CI	<i>p</i> value
Additional opioid dose variables									
ECOG PS at last admission	1.42	1.26–1.60	<0.001	1.42	1.26–1.60	<0.001	1.42	1.26–1.60	<0.001
Sex ^a	0.90	0.71–1.14	0.36	0.90	0.70–1.13	0.37	0.89	0.70–1.13	0.35
Age at death	1.00	0.99–1.01	0.55	1.00	0.99–1.01	0.70	1.00	0.99–1.01	0.63
Bone metastasis at last admission ^b	1.08	0.84–1.38	0.55	1.12	0.89–1.42	0.34	1.11	0.88–1.42	0.36
Additional opioid dose variables									
Opioid dose at last admission	1.00	1.00–1.00	0.41						
Mean opioid dose during last hospitalization				1.00	1.00–1.00	0.53			
Opioid dose at death							1.00	1.00–1.00	0.70

CI confidence interval, ECOG PS Eastern Clinical Oncology Group performance status, RR risk ratio

^a Coded as “1” (male) and “0” (female)

^b Coded as “1” (metastasis) and “0” (no metastasis or not evaluated)

dose at the last chemotherapy (Supplemental Fig. 1a). For the former finding, the risk to survival posed by the rapid increase in the opioid dose as death approached was undeniable in some patients; however, neither a significant relationship between survival time and the rate of increase in opioid dose [10] nor the risk of respiratory depression from opioids [11] has been previously shown. We did not analyze the effects of increasing the opioid dose rate in the present study, because the various and unique ways of dosing cancer patients with opioids made such an analysis too complex. The latter finding might have been the result of differences in the ECOG PS at the last chemotherapy and the age of the patients at death, shown using univariate and multivariate analyses to be predictive factors for survival time (Supplemental Table 7). Although no statistically significant differences were found, opioid nonusers included more patients with a good PS of 0–1 at their last chemotherapy (26 %) and fewer patients with a poor PS of 3–4 (35 %) than opioid users (18 and 44 %, respectively, for users with an OMED <60 mg/day, and 6 and 50 %, respectively, for users with an OMED ≥60 mg/day) (Supplemental Table 3). In addition, opioid nonusers were older at death than opioid users (Supplemental Tables 3, 4, and 5). Therefore, selection bias between the three groups should be noted when

interpreting our survival data. Patients with a better PS might not need to use opioids, while those with a poorer PS might need more opioids. These differences in background and conditions were possibly associated with different survival times.

The second important finding was that, although only 37 % of all patients and 33 % of patients who had been treated with chemotherapy used opioids at the last hospital admission and at the last chemotherapy, respectively, 79 % finally received opioids at death. The current study is the first to report on the practical use of opioids in an acute care hospital setting. As compared with previous studies carried out by palliative care experts, the frequency of opioid use in our study was similar, but the opioid doses were lower [12].

Our study had several limitations. First, we excluded the use of opioid rescue medication at admission, the last chemotherapy, and death from our analyses. Few opioid nonusers used even opioid rescue medication at those times. However, we cannot completely deny the possibility that the use of opioid rescue medication might have affected survival time in the opioid user groups. Second, our study was conducted in relation to care without specialist palliation. Thus, our opioid prescriptions might have been smaller than those administered by palliative care experts. Daily cancer care is

undertaken without specialist palliation in Japan, because there are insufficient palliative care specialists and institutions available [13]. Third, the degree of symptom relief was not assessed in our study, and we are concerned that there may have been insufficient prescribed doses of opioid. Fourth, the introduction of various types of recently developed opioids made our analyses more complicated. Morphine was by far the predominant opioid used in some past studies that have investigated the relationship between opioid use and survival [5, 7–9]. However, many kinds of opioids are available nowadays. There was a considerable difference in the opioid types used between our study and past studies. Fifth, we used two arbitrary parameters without sufficient rationale, namely the last hospitalization period and survival after the last chemotherapy. The former was different from the survival in an institutional hospice and home care hospice program, as analyzed in previous studies. In our study, some patients were admitted to our hospital for the purpose of palliative and end-of-life care, while others were admitted to undergo chemotherapy or emergency treatment. The latter was unprecedented data but was expected to compliment the former. Sixth, screening of distant metastases was not routinely performed at the last chemotherapy and at the last admission. Thus, we are afraid that we might overlook brain and bone metastases in some patients, though our study suggested that those metastases might be associated with opioid use.

In conclusion, the current study suggests that opioid use does not have a negative influence on survival time and should encourage clinicians and patients to use opioids for cancer-related symptom management.

Conflict of interest The authors report no conflicts of interest.

References

1. Morita T, Tsunoda J, Inoue S, Chihara S (2000) Concerns of Japanese hospice inpatients about morphine therapy as a factor in pain management: a pilot study. *J Palliat Care* 16(4):54–58
2. Reid CM, Gooberman-Hill R, Hanks GW (2008) Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. *Ann Oncol* 19(1):44–48
3. Morita T, Miyashita M, Shibagaki M, Hirai K, Ashiya T, Ishihara T, Matsubara T, Miyoshi I, Nakaho T, Nakashima N, Onishi H, Ozawa T, Suenaga K, Tajima T, Akechi T, Uchitomi Y (2006) Knowledge and beliefs about end-of-life care and the effects of specialized palliative care: a population-based survey in Japan. *J Pain Symptom Manag* 31(4):306–316
4. Azoulay D, Jacobs JM, Cialic R, Mor EE, Stessman J (2011) Opioids, survival, and advanced cancer in the hospice setting. *J Am Med Dir Assoc* 12(2):129–134
5. Bercovitch M, Adunsky A (2004) Patterns of high-dose morphine use in a home-care hospice service: should we be afraid of it? *Cancer* 101(6):1473–1477
6. Bercovitch M, Adunsky A (2006) High dose controlled-release oxycodone in hospice care. *J Pain Palliat Care Pharmacother* 20(4):33–39
7. Bercovitch M, Waller A, Adunsky A (1999) High dose morphine use in the hospice setting. A database survey of patient characteristics and effect on life expectancy. *Cancer* 86(5):871–877
8. Morita T, Tsunoda J, Inoue S, Chihara S (2001) Effects of high dose opioids and sedatives on survival in terminally ill cancer patients. *J Pain Symptom Manag* 21(4):282–289
9. Portenoy RK, Sibirceva U, Smout R, Horn S, Connor S, Blum RH, Spence C, Fine PG (2006) Opioid use and survival at the end of life: a survey of a hospice population. *J Pain Symptom Manag* 32(6):532–540
10. Thoms A, Sykes N (2000) Opioid use in last week of life and implications for end-of-life decision-making. *Lancet* 356(9227):398–399
11. Fohr SA (1998) The double effect of pain medication: separating myth from reality. *J Palliat Med* 1(4):315–328
12. Sykes N, Thoms A (2003) The use of opioids and sedatives at the end of life. *Lancet Oncol* 4(5):312–318
13. Morita T, Akechi T, Ikenaga M, Kizawa Y, Kohara H, Mukaiyama T, Nakaho T, Nakashima N, Shima Y, Matsubara T, Uchitomi Y (2005) Late referrals to specialized palliative care service in Japan. *J Clin Oncol* 23(12):2637–2644