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ORIGINAL ARTICLE

Do-not-resuscitate status is correlated with the prescribed use of systemic strong opioid analgesics in patients with terminal cancer: an observational study

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Abstract

Purpose The purpose of this study is to determine the possible correlation between the do-not-resuscitate (DNR) status and the prescribed use of systemic strong opioid analgesics (SSOA) among patients with terminal cancer in Taiwan.

Methods This retrospective cross-sectional study used data from a single tertiary care medical center. We identified patients with terminal cancer who died after signing a DNR order between 2008 and 2016. Subsequently, we reviewed their clinical characteristics, DNR consent type, survival time after DNR declaration, and SSOA dose.

Results Of the 4123 patients enrolled for this study, 1380 (33.5%) had received SSOA before DNR and 2742 (66.5%) had received SSOA after DNR ($p < 0.001$). SSOA doses administered after the DNR order were significantly higher than those administered before the DNR order (median, 78 vs. 60 mg, $p < 0.01$).

Conclusion Patients' DNR status likely influenced physician decision in prescribing SSOA. However, additional studies are necessary to clarify the factors that influence the decision-making of physicians regarding SSOA prescription.

Keywords Do-not-resuscitate · Terminal cancer · Pain · Systemic strong opioid analgesics

Chun-Li Wang and Chia-Yen Lin contributed equally to this work.

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Introduction

From 1982 onward, cancer has been the leading cause of deaths in Taiwan, with annual deaths exceeding 40,000, and this number keeps increasing [1]. Pain prevalence is typically high in patients with cancer, regardless of the disease type or stage [2, 3]. Pain management, therefore, is one of the essential medical treatments to improve the quality of life and end-of-life care. Per the European Society for Medical Oncology Clinical Practice Guidelines for cancer pain management, strong opioids are the mainstay of analgesic therapy in treating moderate-to-severe cancer-related pains [4].

In Taiwan, hospice care is increasingly being accepted by the general population. In 2000, the Legislative Yuan enacted the Hospice Palliative Care Act, which is a landmark change in the autonomy of patients in end-of-life care. This Act gives patients the right to refuse cardiopulmonary resuscitation after the terminal status of their illness is confirmed by at least two specialists. For patients who are too ill to express their wishes, a family surrogate can sign the consent on their behalf according to their previously expressed wish [5]. A pain-free death without unnecessary resuscitation would maintain the dignity of patients who are terminally sick.

Despite the Act and although numerous reviews have reported that there is no evidence that opioids accelerate deaths [6–11], many medical practitioners are affected by the misconceived correlation between using opioids for relieving patients' pain and the concern that opioid use may shorten the survival time of terminally ill patients. A review published in Lancet in 2003 focused on the use of opioids and sedatives at the end of life and highlighted the effect of opioids on survival [12]. The precipitation of death with opioids has not been reported in the literature. Opioid analgesics are often inadequately used for pain control in terminally sick patients. However, during our clinical experiences, we observed that analgesic prescription changes after the do-not-resuscitate (DNR) order is signed. In such cases, their chances of receiving opioids are higher.

This study explored the correlation between the DNR status and the use of systemic strong opioid analgesics (SSOA) in deceased patients with cancer in Taiwan.

Materials and methods

Data source and study patients

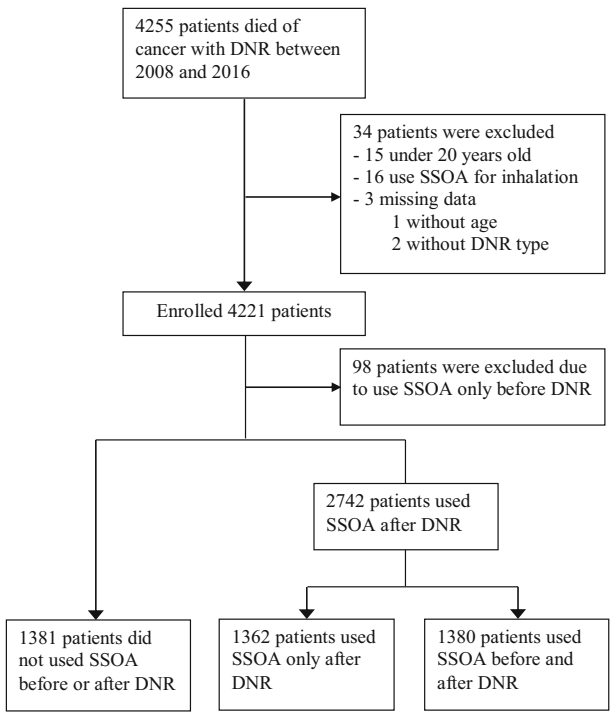
This retrospective cross-sectional study was based on the research database of the Taichung Veterans General Hospital under the hospital management of Clinical Informatics Research and Development Center (registered number F18047). In addition, this study protocol was approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital (IRB number CE18043B).

We analyzed the data of patients who died of cancer and had signed DNR during the same admission course in the hospital from 2008 to 2016. We excluded patients aged < 20 years and those who died within 24 h after signing their DNR. Furthermore, patients using inhalation opioid medication for relieving symptoms of shortness of breath rather than pain were excluded. The use of SSOA for pain control was in oral, injection, or transdermal form.

To investigate the correlation between patient characteristics and DNR status–related SSOA use, we further divided the patients into three subgroups according to their SSOA use: (1) patients without SSOA use neither before nor after DNR; (2) those who had received SSOA both before and after DNR; and (3) those who had received SSOA only after DNR. Patients receiving SSOA only before DNR declaration were excluded. The study design is shown in Fig. 1.

Measures

The following variables were obtained: patient's gender, age at death, cancer diagnosis (including lung cancer, colorectal cancer, liver cancer, oral cancer, breast cancer, prostate cancer, lymphoma/leukemia, gastric cancer,



DNR, do-not-resuscitate; SSOA, systemic strong opioid analgesics.

Fig. 1 The flowchart of the study selection process. DNR, do-not-resuscitate; SSOA, systemic strong opioid analgesics

bladder cancer, esophageal cancer, and gynecological (GYN) cancer), DNR consent type, survival time after DNR declaration, comorbidities, and the individualized record of SSOA.

DNR consent was divided into two categories: (1) the consent forms were signed by patients themselves, including those who had consented in advance and documented their decision in the health insurance card and (2) the patient's DNR was consented by others, including the family proxy, legal surrogate, and doctors serving the best interest of the patient, when the patient had no proxies. Survival time after DNR declaration was measured from the date of DNR documentation to the date of death. Comorbidities included hypertension, type 2 diabetes mellitus, liver cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and seizure.

Data regarding SSOA prescription were extracted from medical records. Items reviewed included DNR type, analgesic administrative route, and dosage for 4 days before and after DNR declaration. The chosen period for evaluation was determined based on the longest SSOA use duration in our hospital (i.e., fentanyl patch, 72–96 h) (Supplementary data Table 1). SSOA prescribed in our hospital from 2008 to 2016 included the following: oral forms of morphine (morphine hydrochloride tablets 10 mg, morphine sulfate tablets 15 mg, morphine sulfate sustained-release F.C. tablets 30 mg, MST CONTINUS tablets 60 mg, and MXL capsule 60 mg), hydromorphone (Jurnista prolonged-release tablets 8 mg), and oxycodone (Oxynorm immediate-release capsules 5 mg, Oxycontin controlled-release tablets 10 mg, and Oxycontin controlled-release tablets 20 mg); injection forms of morphine (morphine hydrochloride 10 and 20 mg/mL); and transdermal forms of fentanyl (Durogesic D-TRANS transdermal patch 12, 25, 50, or 75 mcg/h and fentanyl transdermal patch 25 or 50 mcg/h). Administration frequencies of the fentanyl transdermal patch were once every 2 or 3 days as individualized to each patient. The dose conversions across different analgesics and administration routes were based on the pharmacopeia in our hospital and Opioid Conversion Ratios—Guide to Palliative Care Practice 2016 [13] (Table 1).

Table 1 Dose conversion between morphine and other opioids

	Daily equivalent oral dose (mg)	Conversion ratio
Morphine		
Oral	60	1
Subcutaneous/intramural	30	2:1
Intravenous	20	3:1
Hydromorphone	12	5:1
Oxycodone	30	2:1
Transdermal fentanyl patch (μg/h)		
12	30	
25	60	
50	120	
75	180	

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS version 22.0; International Business Machines Corp., New York, USA). Categorical data were expressed as numbers and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Associations between all categorical variables and SSOA uses were determined through the chi-square and Kruskal–Wallis tests. SSOA doses were analyzed using the McNemar and Wilcoxon signed rank tests. Continuous data were expressed as median and interquartile range. A p value of < 0.05 was considered statistically significant.

Results

A total of 4123 patients who died of cancer and had DNR declarations were identified during the period of 2008–2016. The mean age was 64 years, and 63.7% of them were men. The top five cancer types were lung cancer (24.8%), liver cancer (15.7%), lymphoma/leukemia (8.4%), colorectal cancer (7.5%), and oral cancer (4.4%). Patient characteristics are summarized in Table 2.

Correlation between DNR status and SSOA use

SSOA prescriptions for pain control were significantly different between before and after DNR (33.5% vs. 66.5%, $p < 0.001$). In addition, patients who had received SSOA on the day before DNR declaration were lower than those on the day after (median, 60 mg vs. 78 mg, $p < 0.01$). Similarly, differences in SSOA doses during the days before and after DNR were observed for 2 days (median, 60 vs. 80 mg, $p < 0.001$), 3 days (median, 60 vs. 76.7 mg, $p < 0.001$), and 4 days (median, 60 vs. 77.8 mg, $p < 0.001$) (Fig. 2).

Correlations between patient characteristics and DNR status–related SSOA uses are shown in Table 3. The proportion of patients ≥ 60 years of age was significantly higher in group 1 (71.1%) than in groups 2 and 3 (47.8% and 65.1%, respectively; $p < 0.001$). However, there was no significant difference in DNR status–related SSOA use between genders.

Patients with lung cancer, breast cancer, and colorectal cancer tended to receive more SSOA irrespective of their DNR status. The proportion of patients with lung cancer was significantly lower in group 1 (19.8%) than in groups 2 and 3 (28.0% and 26.7%, respectively; $p < 0.001$). Similarly, the percentage of patients with breast cancer was significantly lower in group 1 (1.2%) than in groups 2 and 3 (2.9% and 3.3%, respectively; $p = 0.001$). Furthermore, the proportion of

Table 2 Characteristics of patients who died of cancer with do-not-resuscitate (DNR) declaration between 2008 and 2016

	n (%)
Total	4123
Gender	
Male	2627 (63.7%)
Female	1496 (36.3%)
Age (years)	
≥ 60	2528 (61.3%)
< 60	1595 (38.7%)
Cancer type[a]	
Lung	1024 (24.8%)
Liver	648 (15.7%)
Lymphoma/leukemia	348 (8.4%)
Colorectal	310 (7.5%)
Oral	182 (4.4%)
Esophageal	158 (3.8%)
Gastric	154 (3.7%)
GYN cancer	115 (2.8%)
Breast	102 (2.5%)
Prostate	87 (2.1%)
Bladder	76 (1.8%)
Other	993 (24.1%)

GYN gynecological

[a] 71 patients had more than one type of cancer, of which 68 patients had 2 cancers and 3 patients had 3 cancers

patients with colorectal cancer was significantly higher in group 2 (9.4%) than in groups 1 and 3 (6.5% and 6.6%, respectively; $p = 0.005$) (Table 3).

Patients with liver cancer and lymphoma/leukemia had a higher chance of not receiving SSOA before or after DNR. The proportions of patients with liver cancer and lymphoma/leukemia in group 1 were 20.5% and 12.5%, respectively, which were significantly higher than those in group 2 (10.9% and 4.5%, respectively) and group 3 (15.8% and 8.4%) ($p < 0.001$). Conversely, we found no such differences in patients with oral, prostate, gastric, bladder, esophageal, and GYN cancers (Table 3).

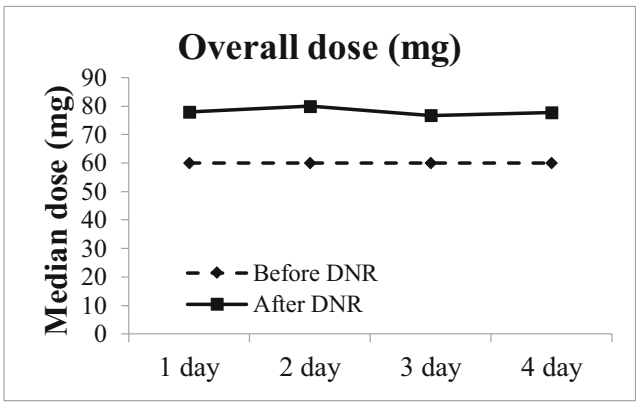


Fig. 2 Overall dose variations during the days before and after do-not-resuscitate (DNR)

Among the 2583 (62.6%) patients who had DNR consent forms signed by their families or surrogates, the highest percentage of patients belonged to group 1 (72.8%), which was significantly higher than that in groups 2 and 3 (57.8% and 57.2%, respectively; $p < 0.001$). Approximately 90.5% of the patients died within 28 days after DNR declaration. There was a significant difference in survival time after DNR declaration among the three groups ($p < 0.001$). In addition, patients with hypertension, type 2 diabetes mellitus, liver cirrhosis, chronic kidney disease, and COPD had a lower proportion of receiving SSOA ($p < 0.001$) (Table 3).

Discussion

The main finding of our study is that the SSOA dose prescribed to (or used by) patients had a correlation with their DNR status. The number of patients with terminal cancer receiving SSOA after DNR declaration was nearly twofold compared with that without DNR declaration. Furthermore, patients who were already treated with SSOA before DNR received higher SSOA doses on the day immediately after DNR. These two results support the hypothesis that DNR status influences the decision of physicians in prescribing SSOA doses. Theoretically and clinically, pain intensities of patients after DNR declaration need not change drastically. Therefore, one may speculate that the pain control of these patients with terminal cancer was way below satisfaction. A review conducted on "good death" or "successful dying" indicated that the most frequently appearing theme for a good death was "preferences for the dying process" followed by "pain-free status" [14]. Furthermore, assessing tools for measuring quality of life (QoL) in patients with cancer, many of the representative questionnaires (e.g., the Palliative Care Quality of Life Instrument, the Assessment of Quality of Life in Palliative Care Instrument, and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire, QLQ-C30) include pain as an essential item [15]. "Pain-free status" is a vital issue for patients with cancer, especially in terminal stages. Therefore, pain control should be applied regardless of their DNR status.

Opioid analgesics could have adverse effects, especially in elderly patients [16, 17]. Older patients taking opioid analgesics had higher percentages of falling accidents and greater hospital mortality [17]. Our results also showed that patients ≥ 60 years old received fewer opiates regardless of the DNR status. Cancer types affect the decision of physicians in prescribing analgesics. The effect may be attributed to different cancer presentations. Cancer pains can be roughly divided into three types according to their origin, namely, somatic, visceral, and neuropathic. Metastasis to the bone is an example of deep

Table 3 Do-not-resuscitate (DNR) status–related ways of systemic strong opioid analgesics (SSOA) used by variables

	Total ($n = 4123$)	Categories of SSOA use			p value
		Group 1 Not use SSOA before or after DNR ($n = 1381$)	Group 2 Use SSOA before and after DNR ($n = 1380$)	Group 3 Use SSOA only after DNR ($n = 1362$)	
Male	2627	907 (65.7%)	853 (61.8%)	867 (63.7%)	0.107
Age (years)	64 ± 14.3	68 ± 13.8	59 ± 13.8	66 ± 14.3	< 0.001
≥ 60	2528	982 (71.1%)	659 (47.8%)	887 (65.1%)	< 0.001
Cancer type					
Lung	1024	274 (19.8%)	386 (28.0%)	364 (26.7%)	< 0.001
Liver	648	283 (20.5%)	150 (10.9%)	215 (15.8%)	< 0.001
Lymphoma/leukemia	348	172 (12.5%)	62 (4.5%)	114 (8.4%)	< 0.001
Colorectal	310	90 (6.5%)	130 (9.4%)	90 (6.6%)	0.005
Oral	182	62 (4.5%)	65 (4.7%)	55 (4.0%)	0.683
Esophageal	158	48 (3.5%)	54 (3.9%)	56 (4.1%)	0.674
Gastric	154	43 (3.1%)	64 (4.6%)	47 (3.5%)	0.086
GYN cancer	115	38 (2.8%)	41 (3.0%)	36 (2.6%)	0.868
Breast	102	17 (1.2%)	40 (2.9%)	45 (3.3%)	0.001
Prostate	87	33 (2.4%)	25 (1.8%)	29 (2.1%)	0.571
Bladder	76	32 (2.3%)	22 (1.6%)	22 (1.6%)	0.275
Other	993	314 (22.7%)	359 (26.0%)	320 (23.5%)	0.109
Type of DNR order					< 0.001
Signed by the patient himself/herself	1540	375 (27.2%)	582 (42.2%)	583 (42.8%)	
Signed by their family or surrogate	2583	1006 (72.8%)	798 (57.8%)	779 (57.2%)	
Survival time after DNR declaration (days)					< 0.001
1–3	930	229 (16.6%)	333 (24.1%)	368 (27.0%)	
4–7	1087	270 (19.6%)	384 (27.8%)	433 (31.8%)	
8–28	1713	709 (51.3%)	529 (38.3%)	475 (34.9%)	
> 28	393	173 (12.5%)	134 (9.7%)	86 (6.3%)	
Comorbidity					
Hypertension	1711	629 (45.5%)	506 (36.7%)	576 (42.3%)	< 0.001
Type 2 DM	1032	403 (29.2%)	276 (20.0%)	353 (25.9%)	< 0.001
Liver cirrhosis	751	328 (23.8%)	173 (12.5%)	250 (18.4%)	< 0.001
CKD	946	392 (28.4%)	228 (16.5%)	326 (23.9%)	< 0.001
COPD	829	331 (24.0%)	212 (15.4%)	286 (21.0%)	< 0.001
Seizure	153	62 (4.5%)	40 (2.9%)	51 (3.7%)	0.086

Values were expressed as numbers and percentages (or mean and SD)

CKD chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *DNR* do-not-resuscitate, *GYN* gynecological, *SSOA* systemic strong opioid analgesics

somatic pain, which is the commonest cause of moderate-to-severe pain. Approximately 75% of the patients with advanced cancer have been noted to experience bone pain [18, 19]. Among all the cancer types, prostate cancer, breast cancer, and lung cancer are the most common malignancies that metastasize to bone, especially in the advanced stage [20, 21]. Consistent with this, our results showed that breast cancer and lung cancer were highly correlated with opiate use regardless of the DNR status.

The association between the DNR consent type and SSOA use indicated that patients who had signed the DNR consent form themselves were prescribed analgesics at a higher rate compared with those whose DNR consent form was signed by a representative. We surmised that this was a consequence of the different states of consciousness. Patients who were conscious were able to sign the consent form and to express their pain clearly. By contrast, undertreatment or mistreatment is more likely

to occur for unconscious patients. Relevance between the survival time after DNR declaration and SSOA use suggested that shorter survival time (≤ 7 days) was related to higher percentages of using SSOA only after DNR. We speculated that it was one crucial factor influencing physician decision or family acceptance. Opiates may have adverse effects, such as altered state of consciousness, respiratory depression, nausea, and vomiting, which may be the reason why physicians avoid prescribing medications to patients. However, terminal cancer patients with a short expected survival time may be able to tolerate the adverse effects of SSOA after discussion with their physicians about the benefits and risks. Our results also showed that the presence of chronic diseases with terminal cancer was related to less opiate use.

This study has several strengths. First, the current study contributes to the literature by examining the SSOA treatment and DNR status among deceased patients with terminal cancer. Second, our study has a large sample size with a long recruitment period. Since the concept of hospice care among patients with terminal cancer had become increasingly popular in Taiwan, opiate underuse aroused physicians' attention to palliative care. However, the increased use of the SSOA may be due to the increased need of the patients for analgesics and for relieving symptoms as for shortness of breath for example.

The limitations of the study are as follows. First, it is a one-center study, thus limiting the generalization of our results. Second, the retrospective design of the study can only demonstrate an association between SSOA use and patient characteristics, but it cannot prove any causal relationship between the two phenomena. Third, in the evaluation of pain intensity, we used the verbal rating scale; the data of which were not extracted due to technical problems. Finally, we did not study the possibilities of inadequate prescriptions underlying the decisions of healthcare providers. Efforts must be made to overcome these limitations.

Conclusion

The decision of whether to treat patients with terminal cancer with SSOA was influenced by patients' DNR status, and doses used were significantly different across patients with different DNR statuses. In addition, age, cancer type, DNR order type, survival period after DNR declaration, and comorbidities influenced physicians' decisions regarding SSOA use and dose prescription. With increasing emphasis of both hospice care and patient dignity in Taiwan, primary healthcare providers can help relieve terminal cancer patients from pain by rational application of SSOA and help them achieve a good death at the end of their life. Further efforts should be made to investigate other factors affecting the decision of physicians.

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Compliance with ethical standards

The study protocol was approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital (IRB number CE18043B).

Conflict of interest The authors declare that they have no conflicts of interest.

Disclaimer The interpretation and conclusions contained herein do not represent those of Taichung Veterans General Hospital.

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