spective assessments. Efficacy was rated as poor, fair, good, or unknown. Safety was defined by the presence or absence of a hangover effect, delirium at night and the next morning (diagnosed by *DSM-IV*), respiratory depression, the reason for treatment withdrawal, and treatment-related death. The face and content validity of these measurement criteria was confirmed by the full agreement of all participating physicians. Interrater reliability was confirmed in 20 patients from two institutions: Cohen's κ, 0.68 for efficacy, 0.65 for hangover, 0.46 for delirium at night, 0.62 for delirium the next morning, and 0.62 for respiratory depression.

The ethical and scientific validity of this study was approved by the Institutional Review Board of the institution of the principal investigator.

Statistical analysis

The initial and maximum doses were defined as the required dose to maintain sleep for one night. Following the previous study,[24] we defined the high-dose requirement of midazolam as the use of a maximum 20 mg per night or more. We calculated the dosage as parenteral midazolam 10 mg = parenteral flunitrazepam 2 mg,[30] and the high-dose requirement of flunitrazepam was thus defined as the use of a maximum 4 mg/day or more.

To compare the backgrounds of the two groups, we compared age, gender, primary site, other medications for insomnia, duration from initial administration to death, and the administration period. To examine the possibility of tolerance, we first calculated Spearman's ρ to explore the correlation of the maximum doses of midazolam and flunitrazepam with the administration periods. Second, we compared the hypnotic escalation index, defined as the daily increase of hypnotic dosage from the initial dose: [(maximal doses initial dose) / initial dose] / administration period $\times$ 100), between patients receiving midazolam and flunitrazepam for more than 2 weeks. Univariate comparisons were performed using the Mann-Whitney U, or χ^2 test (Fisher's exact methods), where appropriate. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 12) for Windows (SPSS Inc., Chicago, IL).

TABLE 1. PATIENT CHARACTERISTICS

	Midazolam group n *104*	*Flunitrazepam group* n *59*	p
Age (years)	66 ± 13	65 ± 13	0.84
Gender			0.42
Male	52% (*n* 54)	59% (*n* 35)	
Female	48% (*n* = 50)	41% (*n* = 24)	
Primary site			0.61
Stomach/esophagus	22% (*n* = 23)	25% (*n* = 15)	
Colon/rectum	16% (*n* 17)	19% (*n* 11)	
Lung	13% (*n* = 13)	19% (*n* = 11)	
Pancreas	11% (*n* 11)	10% (*n* 6)	
Head and neck	8.7% (*n* = 9)	6.8% (*n* = 4)	
Ovary and uterus	6.7% (*n* 7)	6.8% (*n* 4)	
Bladder/prostate/kidney	4.8% (*n* 5)	3.4% (*n* 2)	
Breast	4.8% (*n* = 5)	3.4% (*n* = 2)	
Biliary system	4.8% (*n* 5)	3.4% (*n* 2)	
Liver	3.8% (*n* = 4)	1.7% (*n* = 1)	
Hematological	1.0% (*n* 1)	1.7% (*n* 1)	
Unknown	1.0% (*n* = 1)	0%	
Other	2.9% (*n* 3)	0%	
Other medications for insomnia	34% (*n* = 35)	35% (*n* = 19)	0.85
Haloperidol	*n* 18	*n* 9	
Chlorpromazine	*n* = 4	*n* = 2	
Oral benzodiazepine	*n* 8	*n* 4	
Rectal bromazepam	*n* = 4	*n* = 0	
Secobarbital sodium	*n* 1	*n* 0	
Hydroxyzine	*n* = 0	*n* = 2	
Trazodone	*n* 0	*n* 1	
Median duration from the first administration to death (days)[a]	12 (2–211)	15 (2–209)	0.28

[a]Range in brackets.

RESULTS

The 18 participating palliative care units enrolled a total of 167 patients from April 2002 through July 2005. A total of 1546 patients died in the participating palliative care units during the study period, and 11% ($n = 167$) had received midazolam or flunitrazepam for primary insomnia. Among the institutions, the rate of intravenous midazolam or flunitrazepam use for insomnia ranged from 1.9% to 44% (median, 15%). In total, 104 patients received midazolam (midazolam group) and 59 patients received flunitrazepam (flunitrazepam group). Four patients who received both midazolam and flunitrazepam were excluded from further analyses.

There were no significant differences in age, gender, primary site, other medications for insomnia, and duration from initial administration to death between the two groups (Table 1).

Administration period dose and method

The median administration periods were 6 and 9 days for midazolam and flunitrazepam, respectively (Table 2). There were no significant differences in the administration periods between the groups. The median initial and maximum doses were 10 mg per night and 18 mg per night for midazolam, and 2 mg per night and 2 mg per night for flunitrazepam, respectively. There were no significant differences in the initial doses as parenteral midazolam equivalent between the groups. The number of patients who required high-dose benzodiazepines was significantly higher in the midazolam group than in the flunitrazepam group (50% versus 15%).

The maximum doses were significantly correlated with patient age in the midazolam group ($\rho = -0.25$, $p = 0.013$), but there was no significant correlation in the flunitrazepam group ($\rho = -0.20$, $p = 0.126$). The maximum doses were significantly correlated with the initial doses in the midazolam ($\rho = 0.64$, $p < 0.001$) and the flunitrazepam groups ($\rho = 0.47$, $p < 0.001$). There were significant differences in the administration methods between the groups ($p < 0.001$).

Efficacy and safety

Although the midazolam group trended towards a better sleep than the flunitrazepam group, the difference did not reach statistical significance. There were no statistically significant differences in the prevalence of hangover, delirium at night, delirium the next morning, treatment withdrawal, and treatment-related death, while the flunitrazepam group experienced respiratory depression significantly more frequently than the midazolam group (Table 3).

There were no significant differences in efficacy and the safety in each administration protocol (Table 4).

Tolerance

The correlation between the maximum doses and the administration periods was higher in the midazolam group than in the flunitrazepam group ($\rho = 0.52$, $p < 0.0001$ versus $\rho = 0.39$, $p = 0.003$).

Table 5 shows that, in patients treated for 14 days or longer, the frequency of high-dose benzodiazepine requirements and the hypnotic escalation index percent were significantly higher in the midazolam group than in the flunitrazepam group.

TABLE 2. ADMINISTRATION PERIOD DOSE AND METHOD

	Midazolam group n *104*	*Flunitrazepam group* n *59*	P
Median administration period (days)[a]	6 (1–207)	9 (1–206)	0.11
Median initial dose (mg/night)[a]	10 (1.8–140)	2 (0.2–2.5)	
Median maximum dose (mg/night)[a]	18 (3–173)[c]	2 (0.5–6)	
High-dose requirement (%)[b]	50% ($n = 51$)	15% ($n = 9$)	<0.001
Median hypnotic escalation index (%)[a,d]	3.1 (0–333)[c]	1.3 (0–108)	0.33
Administration method			<0.001
Continuous infusion all night	70% (n 73)	24% (n 14)	
Infusion for one or two hours	21% ($n = 22$)	42% ($n = 25$)	
Infusion until the patient fell asleep	9% (n 9)	34% (n 20)	

[a]Range in brackets.
[b]Maximum parenteral midazolam equivalent ≥ 20 mg/night
[c]Due to a missing value, 103 patients were analyzed.
[d]Hypnotic escalation index % = percentage daily increase of initial dose = [(maximal doses–initial dose)/initial dose]/administration period × 100.

TABLE 3. EFFICACY AND SAFETY OF MIDAZOLAM AND FLUNITRAZEPAM

	Midazolam group n = *104*	*Flunitrazepam group* n = *59*	p
Efficacy			0.084
Poor	6.7% (*n* = 7)	15% (*n* = 9)	
Fair	28% (*n* 29)	37% (*n* 22)	
Good	63% (*n* = 66)	44% (*n* = 26)	
Safety			
Hangover	34% (*n* = 35)	19% (*n* = 11)	0.094
Delirium			
Night	12% (*n* = 12)	10% (*n* = 6)	1.0
Next morning	11% (*n* 11)	15% (*n* 9)	0.33
Respiratory depression	3.8% (*n* = 4)	17% (*n* = 10)	0.0073
Death	0%	0%	1.0
Treatment withdrawal	4.8% (*n* = 5)	1.7% (*n* = 1)	0.41
Reasons			
Delirium	2.8% (*n* = 3)	1.7% (*n* = 1)	
Respiratory depression	1.0% (*n* 1)		
Fall from bed	1.0% (*n* = 1)		

Some percentages do not add up to 100% due to missing values.

Cost effectiveness

The median cost of initial and maximum administration was 176 yen (range, 32–2464) and 308 yen (range, 53–3045) for midazolam and 165 yen (range, 17–206) and 165 yen (range, 41–495) for flunitrazepam, respectively. The costs of the initial and maximum administration were significantly higher in the midazolam group than in the flunitrazepam group ($p < 0.001$).

DISCUSSION

The most important finding of this study was the comparison of efficacy and safety (hangover effect, delirium at night and the next morning, and respiratory depression) of the initial administration of intravenous midazolam and flunitrazepam. Although this was not a randomized controlled trial, there were no significant differences in background data and initial doses as parenteral midazolam equivalent[30] between the two groups, and thus we believe the comparisons of the treatment effects were reasonable. There were no statistically significant differences between midazolam and flunitrazepam in the efficacy of the initial administration of these medications, although more patients who received midazolam had a better sleep than those given flunitrazepam. These findings suggest that both intravenous benzodiazepines are essentially effective in the terminal stage.

There was no significant difference between the two groups with respect to their hangover effect. We would expect that the hangover effect might be more frequent in patients receiving flunitrazepam than midazolam, because of the difference of their biologic half-life. Contrary to our initial assumption, the percentage hangover effect in the midazolam group was essentially the same as in the flunitrazepam group. A potential interpretation is that continuous infusion until morning was performed more often in the midazolam group than in the flunitrazepam group, which might enhance the possibility of the hangover effect in the midazolam group. There were no significant differences in the hangover effect in each administration protocol; however, unfortunately, in our study, the number of subjects was small, and thus we do not have statistical power to test this hypothesis.

In addition, this study revealed no difference in the prevalence of delirium at night and the next morning between midazolam and flunitrazepam. This finding is also contrary to our initial assumption that short-acting benzodiazepines cause delirium more frequently than long-acting benzodiazepines.[31]

On the other hand, respiratory depression was significantly more frequently observed in the flunitrazepam group than in the midazolam group. In the palliative care setting, continuous subcutaneous infusion of midazolam has been reported, and almost all reports[13–15,17,34] emphasized the safety of midazolam, especially with regard to respiratory depression and cardiovascular compromise. Compared to these studies, the incidence of respiratory depression in our study seemed relatively high. A potential interpretation includes the strict definition of respiratory depression in our study, the differences in the infusion protocol, and

TABLE 4. COMPARISON OF ADMINISTRATION PROTOCOL

Administration protocol	*Midazolam group* n = *104*				*Flunitrazepam group* n = *59*			
	Continuous infusion all night n = *73*	*Infusion for one or two hours* n = *22*	*Infusion until the patient fell asleep* n = *9*	p	*Continuous infusion all night* n = *14*	*Infusion for one or two hours* n = *25*	*Infusion until the patient fell asleep* n = *20*	p
Efficacy								
Poor	55% (*n* 4)	9.1% (*n* 2)	11% (*n* 1)	0.98	14% (*n* 2)	24% (*n* 6)	5.0% (*n* 1)	0.62
Fair	27% (*n* = 20)	32% (*n* = 7)	22% (*n* = 2)		29% (*n* = 4)	32% (*n* = 8)	50% (*n* = 10)	
Good	67% (*n* 49)	50% (*n* 11)	67% (*n* 6)		57% (*n* 8)	40% (*n* 10)	40% (*n* 8)	
Safety								
Hangover	36% (*n* 26)	32% (*n* 7)	22% (*n* 2)	0.91	29% (*n* 4)	20% (*n* 5)	10% (*n* 2)	0.64
Delirium								
Night	14% (*n* 10)	9.1% (*n* 2)	0%	0.81	21% (*n* 3)	8.0% (*n* 2)	5.0% (*n* 1)	0.58
Next morning	14% (*n* = 10)	0%	11% (*n* = 1)	0.31	21% (*n* = 3)	4.0% (*n* = 1)	5.0% (*n* = 1)	0.40
Respiratory depression	1.4% (*n* 1)	4.5% (*n* 1)	22% (*n* 2)	0.09	0%	16% (*n* 4)	30% (*n* 6)	0.18
Death	0%	0%	0%	0.98	0%	0%	0%	0.98
Treatment withdrawal	2.7% (*n* = 2)	9.1% (*n* = 2)	11% (*n* = 1)	0.77	0%	0%	5.0% (*n* = 1)	0.82
Delirium	2.7% (*n* 2)	4.5% (*n* 1)	0%		0%	0%	0%	
Respiratory depression	0%	0%	11% (*n* = 1)		0%	0%	5.0% (*n* = 1)	
Fall from bed	0%	4.5% (*n* = 1)	0%		0%	0%	0%	

Some percentages do not add up to 100% due to missing values.

target symptoms (i.e., primary insomnia versus refractory symptoms close to death). Of note was that no fatal or clinically relevant respiratory depression was observed in both groups, and thus the findings indicate that these treatments were generally safe.

The second important finding was the comparison of the possibility of tolerance development between midazolam and flunitrazepam. Compared to the flunitrazepam group, significantly more patients required high-dose benzodiazepine and the hypnotic escalation index was significantly higher in the midazolam group. These results suggest that midazolam is more likely to develop pharmacologic tolerance to the clinical effects of insomnia. In several studies[14,15] longer use of midazolam increased the risk of tolerance development: Morita et al.[24] reported that the maximum dose of midazolam was significantly higher in patients treated for longer than 14 days. The findings in this study support the previous observation that longer use of midazolam increases the risk of tolerance development, and thus we suggest that flunitrazepam should be tried for patients with a predicted survival of longer than 2 weeks.

Of note was that the use prevalence of intravenous midazolam and flunitrazepam for insomnia was relative low in this study. Prevalence estimates for sleep disturbance in palliative care units range from 23% to 70%.[32,33] The median prevalence rate of treatments in this study was lower than the assumed prevalence of primary insomnia. The probable interpretation is that intravenous drip hypnotics are not necessary because the oral or rectal route is available until just before

TABLE 5. REQUIREMENT OF HIGH-DOSE BENZODIAZEPINES AND HYPNOTIC ESCALATION INDEX (ADMINISTRATION PERIOD ≥14 DAYS)

	Midazolam group n 27	*Flunitrazepam group* n 26	p
High-dose benzodiazepine requirement[a]	85% (*n* = 23)	15% (*n* = 4)	<0.001
Median hypnotic escalation index (%)[b]	11 (0–262)	2.6 (0–160)	0.015

[a]Maximum parenteral midazolam equivalent ≥ 20 mg/night

[b]Hypnotic escalation index % = percentage daily increase of initial dose = [(maximal dose–initial dose)/initial dose]/administration period × 100.

death in many patients with cancer. In addition, the wide range among institutions in the use of parenteral benzodiazepines indicates differences in the indications for these treatments. More discussion about the indications for these treatments and an investigation of other administration routes for insomnia is needed.

Despite several strengths, including a multicenter study on a relatively large number of patients using standardized evaluation methods according to strict chart descriptions, this study has several limitations. First, the main limitation is the ad-hoc retrospective and observer rating of outcomes. We believe, however, that this is not a fatal flaw of this study, because (1) there is a lack of validated measurement tools available in this setting, (2) interrater reliability was adequate, and (3) we adopted strict criteria for ratings following the actual chart descriptions. Second, it was difficult to completely evaluate the effects of other medications for insomnia. We believe that, because there was no statistically significant difference in the use of comedications between the groups, this did not seriously influence the conclusions. Third, we excluded patients receiving benzodiazepines to palliate any physical and psychical symptoms other than primary insomnia. The findings thus cannot be automatically generalized to patients receiving benzodiazepines for palliative sedation therapy. Finally, we could not unify the administration protocol due to the large variance in clinical practice in the institutions.

In conclusion, intravenous midazolam and flunitrazepam appeared to show almost identical efficacy and safety for primary insomnia, but flunitrazepam is cheaper and shows lower tolerance. A future prospective study is necessary.

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REFERENCES

1. Mercadante S, Girelli D, Casuccio A: Sleep disorders in advanced cancer patients: Prevalence and factors associated. Support Care Cancer 2004;12:355–359.
2. Davidson JR, MacLean AW, Brundage MD, Schulze K: Sleep disturbance in cancer patients. Soc Sci Med 2002;54:1309–1321.
3. Savard J, Morin CM: Insomnia in the context of cancer: A review of a neglected problem. J Clin Oncol 2001;19:895–908.
4. Stiefel F, Ravavi D: Psychotropics in supportive care: First assess, then prescribe. Support Care Cancer 1999;7:371–372.
5. Goldberg RJ, Mor V: A survey of psychotropic use in terminal cancer patients. Psychosomatics 1985;26:745–751.
6. Matsuo N, Morita T: Intravenous infusion of midazolam and flunitrazepam for insomnia on Japanese palliative care units. J Pain Symptom Manage 2005;30:301–302.
7. Mercadante S, Ferrera P, Girelli D, Casuccio A: Patients' and relatives' perceptions about intravenous and subcutaneous hydration. J Pain Symptom Manage 2005;30:354–358.
8. 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: Knowledge and beliefs about end-of-life care and the effects of specialized palliative care: A population-based survey in Japan. J Pain Symptom Manage 2006;31:306–316.
9. Chiu TY, Hu WY, Chuang RB, Cheng YR, Chen CY, Wakai S: Terminal cancer patients' wishes and influencing factors toward the provision of artificial nutrition and hydration in Taiwan. J Pain Symptom Manage 2004;27:206–214.
10. Smales EA, Sanders HG: Flunitrazepam in terminal care. Lancet 1989;26:501.
11. Smales OR, Smales EA, Sanders HG: Flunitrazepam in terminal care. J Paediatr Child Health 1993;29:68–69.
12. Morita T, Chinone Y, Ikenaga M, Miyoshi M, Nakaho T, Nishitateno K, Sakonji M, Shima Y, Suenaga K, Takigawa C, Kohara H, Tani K, Kawamura Y, Matsubara T, Watanabe A, Yagi Y, Sasaki T, Higuchi A, Kimura H, Abo H, Ozawa T, Kizawa Y, Uchitomi Y; Japan Pain, Palliative Medicine, Rehabilitation, and Psycho-Oncology Study Group: Ethical validity of palliative sedation therapy: A multicenter, prospective, observational study conducted on

specialized palliative care units in Japan. J Pain Symptom Manage 2005;30:308–319.
13. Amesbury BDW, Dunphy KP: The use of subcutaneous midazolam in the home care setting. Palliat Med 1989;3: 299-301.
14. Bottomley DM, Hanks GW: Subcutaneous midazolam infusion in palliative care. J Pain Symptom Manage 1990;5: 259–261.
15. Burke AL, Diamond PL, Hulbert J, Yeatman J, Farr EA: Terminal restlessness-Its management and the role of midazolam. Med J Aust 1991;155:485–487.
16. Holdsworth MT, Adams VR, Chavez CM, Vaughan LJ, Duncan MH: Continuous midazolam infusion for the management of morphine-induced myoclonus. Ann Pharmacother 1995;29:25–29.
17. McNamara P, Minton M, Twycross RG: Use of midazolam in palliative care. Palliat Med 1991;5:244–249.
18. Ramani S, Karnad AB: Long-term subcutaneous infusion of midazolam for refractory delirium in terminal breast cancer. South Med J 1996;89:1101–1103.
19. Vermeeren A: Residual effects of hypnotics: Epidemiology and clinical implications. CNS Drugs 2004;18:297–328.
20. Morita T, Chinone Y, Ikenaga M, Miyoshi M, Nakaho T, Nishitateno K, Sakonji M, Shima Y, Suenaga K, Takigawa C, Kohara H, Tani K, Kawamura Y, Matsubara T, Watanabe A, Yagi Y, Sasaki T, Higuchi A, Kimura H, Abo H, Ozawa T, Kizawa Y, Uchitomi Y; Japan Pain, Palliative Medicine, Rehabilitation, and Psycho-Oncology Study Group: Efficcy and safety of palliative sedation therapy: A multicenter, prospective, observational study conducted on specialized palliative care units in Japan. J Pain Symptom Manage 2005;30:320–328.
21. Singer PA, Martin DK, Kelner M: Quality end of life care. Patients' perspectives. JAMA 1999;281:163–168.
22. Steinhauser KE, Clipp EC, Mc Neilly M, et al. In search of a good death: observations of patients, families, and providers. Ann Intern Med 2000;132:825–832.
23. Steinhauser KE, Christakis NA, Clipp EC, McNeilly M, McIntyre L, Tulsky JA: Factors considered important at the end of life by patients, family, physicians, and other care providers. JAMA 2000;284:2476–2482.
24. Morita T, Tei Y, Inoue S: Correlation of the dose of midazolam for symptom control with administration periods: The possibility of tolerance. J Pain Symptom Manage 2003;25:369–375.
25. Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, Schein RM, Spevetz A, Stone JR: Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: A executive summary. Crit Care Med 1995;23:1596–1600.
26. Shelly Mp, Sultan MA, Bodenham A, Park GR: Midazolam infusions in critically ill patients. Eur J Anaesth 1991;8:21–27.
27. Tobias JD: Tolerance, withdrawal, and physical dependency following long term sedation and analgesia of children in Pediatric ICU. Crit Care Med 2000;28:2122–2132.
28. Sjovall S, Kanto J, Kangas L, Pakkanen A: Comparison of midazolam and flunitrazepam for night sedation. Anaesth 1982;37:924–928.
29. Lingjaerde O, Bratlid T, Westby OC, Gordeladze JO: Effect of midazolam, flunitrazepam, and placebo against mid winter insomnia in northern Norway. Acta Psychiatr Scand 1983;67:118–129.
30. Dundee JW, Halliday NJ, Harper KW, Brogden RN: Midazolam. A review of its pharmacological properties and therapeutic use. Drugs 1984;28:519–543.
31. Soldatos CR, Kales A, Bixler EO: Behavioral side effects of benzodiazepine hypnotics. Clin Neuropharmacol 1985;8 Suppl 1:S112–7.
32. Ng K, von Gunten CF: Symptoms and attitudes of 100 consecutive patients admitted to an acute hospice/palliative care unit. J Pain Symptom Manage 1998;16:307–316.
33. Hugel H, Ellershaw JE, Cook L, Skinner J, Irvine C: The prevalence, key causes and management of insomnia in palliative care patients. J Pain Symptom Manage 2004;27: 316–321.
34. Stiefel F, Fainsinger R, Bruera E: Acute confusional states in patients with advanced cancer. J Pain Symptom Manage 1992;7:94–98.

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APPENDIX. DEFINITIONS OF EACH MEASUREMENT

Efficacy	
Poor	Chart descriptions of 1) patient expressions such as "I didn't sleep.", "I didn't sleep at all.", "I didn't sleep and was distressed.", "I didn't sleep soundly.", "I didn't get to sleep easily.", "I had a bad dream." Or, 2) physician or nurses' records such as "The patient tossed and turned all night.", "The patient woke up off and on.", "The patient moved during the night.", "Reconsideration of hypnotics is necessary.", "no sleep", "not very much sleep", "slept lightly", "The patient was delirious."
Fair	Chart descriptions of 1) patient expressions such as "I slept so-so.", "I slept a little.", "I generally slept.", "I slept slightly better than yesterday." Or, 2) physician or nurses' records such as "The patient mostly slept although he woke up or moved during the night."
Good	Chart descriptions of 1) patient expressions such as "I slept.", "I had a good sleep.", "I slept very well.", "I slept soundly." Or, 2) physician or nurses' records such as "The patient didn't wake up and didn't move during the night."
Unknown	There was no description about sleep.
Hangover	
Presence	Chart descriptions of 1) patient expressions such as "I am drowsy.", "I am sleepy.", "My mind is not clear.", "I have a hangover." Or, 2) physician or nurses' records such as "drowsy", "somnolent", "The patient sleeps until past 9 am.", "The patient dozes off.", "The patient cannot eat breakfast because of sleepiness.", "The patient looks sleepy.", "There is a sign of hangover.", "The patient doesn't wake up.", "The patient dozes off while talking.", "The patient cannot urinate because of sleepiness."
Absence	Chart descriptions of 1) patient expressions such as "My mind is very clear.", "I awoke refreshed.". Or, 2) physician or nurses' records such as "The patient awoke refreshed", "The patient is very alert."
Unknown	There was no description about sleepiness next morning.
Respiratory depression	
Presence	Physician or nurses' records such as "apnea", "respiratory arrest", "decreased respiratory rate", "respiratory depression".
Absence	There was not above description.

Original Article

Terminal Delirium: Recommendations from Bereaved Families' Experiences

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Abstract

Although delirium is a common complication in terminally ill cancer patients and can cause considerable distress for family members, little is known about effective care strategies for terminal delirium. The primary aims of this study were 1) to clarify the distress levels of bereaved families and their perceived necessity of care; and 2) to explore the association between these levels and family-reported professional care practice, family-reported patient behavior, and their interpretation of the causes of delirium. A multicenter questionnaire survey was conducted on 560 bereaved family members of cancer patients who developed delirium during their final two weeks in eight certified palliative care units across Japan. We obtained 402 effective responses (response rate, 72%) and, as 160 families denied delirium episodes, 242 responses were analyzed. The bereaved family members reported that they were very distressed (32%) and distressed (22%) about the experience of terminal delirium. On the other hand, 5.8% reported that considerable or much improvement was necessary, and 31% reported some improvement was necessary in the professional care they had received. More than half of the respondents had ambivalent wishes, guilt and self-blame, and worries about staying with the patient. One-fourth to one-third reported that they felt a burden concerning proxy judgments, burden to others, acceptance, and helplessness. High-level emotional distress and family-perceived necessity of improvement were associated with a younger family age; male gender; their experience of agitation and incoherent speech; their interpretation of the causes of delirium as pain/physical discomfort, medication effects, or

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mental weakness/death anxiety; and their perception that medical staff were not present with the family, not respecting the patient's subjective world, not explaining the expected course with daily changes, and not relieving family care burden. In terminal delirium, a considerable number of families experienced high levels of emotional distress and felt some need for improvement of the specialized palliative care service. Control of agitation symptoms with careful consideration of ambivalent family wishes, providing information about the pathology of delirium, being present with the family, respecting the patient's subjective world, explaining the expected course with daily changes, and relieving family care burden can be useful care strategies. J Pain Symptom Manage 2007;34:579–589.

Key Words
Palliative care, delirium, family, neoplasms, end-of-life care

Introduction

Delirium or cognitive disorder occurs in 68%–90% of terminally ill cancer patients just before death.[1–5] Although cognitive impairment can sometimes be labeled as part of the "natural" dying process, delirium-related symptoms can cause great distress to both patients and family members.[6,7] According to one prospective observation study of 75 family members of delirious cancer patients, 76% of family members showed high levels of psychological distress as a result of the delirium symptoms.[6] A questionnaire survey involving 300 bereaved Japanese families revealed that more than two-thirds perceived all delirium-related symptoms other than somnolence as distressing or very distressing.[7] These results indicate that, given that one of the primary goals of integrated palliative care is to alleviate family suffering, active support for the family members of delirious terminal patients is of great importance.

Understanding the experience of families of delirious terminally ill patients is vital to explore effective care strategies. To our knowledge, however, despite many experience-based recommendations by palliative care specialists,[8–11] only a few studies have explored the actual experiences of families in the terminal stage.[12–14] Our previous qualitative study revealed that the families experienced various phenomena other than psychiatric symptoms, had a range of emotions, interpreted the delirium variously, and listed some specific useful support strategies in caring terminal delirium.[14] Although this study provides a potentially useful insight, generalizability is limited due to a lack of quantitative data.

The primary aim of the current study was thus to: 1) clarify the distress levels of bereaved families and their perceived necessity of care related to terminal delirium; and 2) explore the association between these levels and family-reported professional care practice, family-reported patient behavior, and their interpretation of the causes of delirium.

Methods

This was a cross-sectional, anonymous, multicenter survey of the bereaved families of cancer patients who had been admitted to eight palliative care units in Japan. We mailed questionnaires to bereaved families in February 2006, and again in March 2006 to nonresponding families. If the families did not want to participate in the survey, they were requested to return the questionnaire with "no participation" indicated, and the second questionnaire was not mailed. The participating institutions were conveniently selected from 150 certified palliative care units. We acknowledged the potential sampling bias, but decided to use convenient institutions due to the practical difficulties of obtaining participants from all palliative care units, and because a relatively large number of patients can minimize the risk of sampling bias.

Subjects

Primary palliative care responsible physicians identified potential participants following these inclusion criteria: 1) bereaved adult family members of an adult cancer patient (one family member was selected for each

patient), with delirium during the final two weeks of life (based on a retrospective chart review and using Diagnostic and Statistical Manual of Mental Disorders, 4 (DSM-IV) criteria[15]), 2) capable of replying to a self-reported questionnaire, 3) aware of the diagnosis of malignancy, and 4) no serious psychological distress recognized by the primary palliative care physicians. The last criterion was adopted in the same way as in our previous surveys,[16,17] on the assumption that primary palliative care physicians could identify families who would suffer serious psychological distress from this survey, because they were closely involved in caring for their relative in an inpatient care setting with a mean admission period of 43 days. We excluded patients with preexisting symptomatic organic brain pathology (i.e., brain metastasis, infarction) or psychiatric disorders other than delirium (i.e., psychosis, dementia), because the psychiatric symptoms might influence the results. To minimize the possibility of sampling bias among institutions, we compared the percentages of patients diagnosed with delirium per all dead patients and the percentages of patients excluded from this study due to the last criterion among the institutions.

Each hospital was requested to consecutively enroll the families of 90 patients who developed delirium and died in 2005 (one institution with clinical activity of less than one year enrolled all patients treated there).

The completion and return of the questionnaire was regarded as consent to participate in this study. Ethical and scientific validity was confirmed by the institutional review board of each hospital.

Measurement Tools

Questionnaire. A questionnaire (available from the authors upon request) was developed for this study based on a systematic literature review,[6–14,18–23] our previous qualitative study based on in-depth interviews with 20 bereaved family members,[14] and discussions among the authors. Content validity was assessed by full agreement of the authors, and the face validity of the questionnaire was confirmed by a pilot test.

As background data, the families reported their ages, genders, relationships to the patient, and intervals from patient death to the study. In the first part of the questionnaire, we asked the respondents whether they thought the patient was delirious or not, because in our previous interview study, 17 of 37 families denied delirium despite diagnostic confirmation based on chart review.[14] Delirium was paraphrased in the questionnaire as "the rapid development of difficulty in concentration, forgetfulness, disorientation about time and place, hallucinations and delusions, incoherent speech, clouding of consciousness and difficulty in communicating, emotional instability, reversal of daytime and nighttime activities (drowsiness during the day and wakefulness during the night), and inconsistent behavior, with these conditions changing even within a day." We carefully developed this introduction section on the basis of the DSM-IV criteria through full agreement among the author liaison psychiatrists and palliative care specialists.

The primary endpoints of this study were family-perceived emotional distress related to terminal delirium and the necessity for improvement in professional care at that time. Due to the lack of validated instruments, these outcome parameters were developed for this study following previous surveys.[16,17] The level of family-perceived distress was evaluated by the response to "How distressing was the patient's delirium for you?," rated on a 5-point scale from 1, "no distress at all" to 5, "very distressing." The necessity for improvement was evaluated by the answer to "How much improvement do you think is necessary in the care for delirium?," rated on a 4-point scale as 1, "no need for improvement," 2, "need for some improvement," 3, "need for considerable improvement," and 4, "need for much improvement." To explore the families' emotions, we asked the respondents to rate their degree of agreement with 16 statements to describe their feelings on a 5-point Likert-type scale of 1, "disagree," to 5, "strongly agree" (Table 2). In addition, we asked the respondents to rate their degree of agreement with eight potential meanings of delirium for the family member on a 5-point Likert-type scale of 1, "disagree," to 5, "strongly agree" (Table 4).

The families were further requested to report factors potentially contributing to these primary endpoints. They were conceptualized prior to the survey and classified into the

following categories: 1) family-reported patient behavior (rated on a 5-point Likert-type scale of 1: none, 2: occasionally, and 3: often) (Table 3); 2) families' interpretation of the causes of delirium (examined by the degree of agreement on a 5-point Likert-type scale of 1: disagree to 5: strongly agree) (Table 4); 3) family-reported professional care practice (examined using the yes-no format) (Table 5); and 4) the family care subscale of the Care Evaluation Scale.[24]

The Care Evaluation Scale is an originally validated 28-item questionnaire to measure bereaved family-perceived necessity of improvement in end-of-life care;[24] its reliability and validity have been well established. The family care subscale was designed to quantify the family-perceived necessity of improvement in care to relieve the family care burden. A lower score indicated a greater need for improvement (possible range, 0—10).

Chart Review Data. Primary palliative care physicians recorded the patient backgrounds (age, gender, primary tumor site, admission periods, and the type and severity of delirium on item 9 of the Memorial Delirium Assessment Scale—Japanese version[25]).

Analyses

To describe the estimated frequency of the phenomenon observed, we calculated the 95% confidence intervals (CI) for each figure.

For comparisons, the respondents were classified into two groups: family members who rated their distress level as "very distressed" (high-level distress) and others (low-level distress); and family members who rated the necessity for improvement as "much," "considerable," or "some" (defined as a high level of perceived necessity for improvement) and others (low level). These cutoff points were determined on the basis of the actual data distribution to divide the whole sample into appropriate sizes of comparison groups.

To explore the underlying structure of the families' emotions (Table 2), we reported factor-loading values by exploratory factor analysis with promax rotation on emotion-related items, and calculated Cronbach's alpha. Two ambivalent items with different meanings within one sentence were excluded from this analysis.

To explore the determinants of the levels of family-perceived distress and necessity for improvement, we initially screened: 1) demographic variables (patient age, gender, admission periods, responding family member age, gender, relationship to the patient, interval from patient death to study, health status in the last week, availability of someone with whom they could consult about the patient, and someone who could care for the patient instead of them); 2) type and severity of delirium (measured using item 9 of the Memorial Delirium Assessment Scale by the primary physicians); 3) family-reported patient behavior (Table 3); 4) families' interpretation of the causes of delirium (Table 4); 5) family-reported professional care practice (Table 5); and 6) the family care subscale of the Care Evaluation Scale. Univariate analyses were performed using Student's *t*-test or the Chi-square test, where appropriate. Multiple logistic regression analyses were then performed in a forward-elimination fashion. All potential predictors with statistical significance by univariate analyses were entered in the equation as independent variables, and we reported the factors that achieved $P < 0.1$ because they had a clinically meaningful interpretation despite marginal statistical significance.

All analyses were performed using the Statistical Package for the Social Sciences (version 11.0).

Results

Of 984 patients who died during this study period, 672 patients (68%) were diagnosed with delirium during the final two weeks of life. Of them, 53 patients had preexisting symptomatic organic brain or psychiatric disorders, and 19 patients had no competent adult family members available. Of the remaining 600 patients, we excluded 40 bereaved family members (6.7%) due to serious psychological distress recognized by primary physicians. Among the institutions, the percentages of patients diagnosed with delirium per all deceased patients ranged from 47% to 87% (three institutions below 70%), and the percentages of patients excluded from this study due to psychological reasons ranged from 0% to 12% (all but one institution below 7.0%).

We thus sent questionnaires to 560 families, 10 of which were returned as undeliverable. Four hundred twenty-seven families returned questionnaires (response rate, 78%, 427/550). Of them, nine families refused to participate, and 16 responses were excluded due to missing data in primary endpoints. Thus, we obtained 402 effective responses (effective response rate, 73%, 402/550). As 160 families denied delirium episodes, further analyses were performed on 242 responses. Table 1 summarizes the backgrounds of patients and bereaved family members. The subtypes of delirium were hypoactive, 29% ($n=70$); hyperactive, 48% ($n=117$); and mixed, 20% ($n=48$). Symptom severity was mild, 39% ($n=95$); moderate, 47% ($n=114$); and severe, 11% ($n=26$) on item 9 of the Memorial Delirium Assessment Scale.

Table 1
Backgrounds

	% (*n*)
Patients	
Age (mean ± SD)	69 ± 12
Sex	
Male	64 (155)
Female	36 (87)
Primary sites	
Lung	26 (62)
Stomach	13 (31)
Colon, rectum	11 (27)
Pancreas, bile duct	12 (29)
Liver	5.3 (13)
Neck	6.2 (15)
Uterus, ovary	4.1 (10)
Bladder, kidney, prostate	7.9 (19)
Breast	3.3 (8)
Esophagus	2.5 (6)
Unknown	2.1 (5)
Others	7.0 (17)
Admission periods (d) (mean ± SD)	43 ± 48 (median, 28)
Bereaved families	
Age (mean ± SD)	58 ± 13
Sex	
Male	25 (60)
Female	74 (178)
Relationship	
Spouse	55 (132)
Child	30 (72)
Parents	1.7 (4)
Siblings	4.1 (10)
Others	9.1 (22)
Interval from patient death (mo) (mean ± SD)	12 ± 13 (median, 11)
In the last week	
Health status	
Good	74 (180)
Poor	24 (58)
Availability of person with whom the respondent consulted about the patient	91 (221)
Availability of person who cared for the patient instead of the respondent	71 (171)
Frequency of staying with the patient	
Every day	77 (186)
4–6 days/wk	12 (29)
1–3 days/wk	8.7 (21)

Some data do not add up to 100% due to missing values.

Overall Levels of Family-Reported Distress and Necessity for Improvement

The degree of family-reported distress was very distressing (32% [95% CI: 26,38], $n=77$), distressing (22% [95% CI: 17,28], $n=53$), slightly distressing (31% [95% CI: 25,37], $n=74$), not so distressing (10% [95% CI: 7.0,15], $n=25$), and not distressing at all (5.4% [95% CI: 3.0-9.0], $n=13$). The necessity of improvement in delirium care as rated by the family members was much improvement needed (0.8% [95% CI: 0,3.0], $n=2$), considerable improvement needed (5.0% [95% CI: 3.0,9.0], $n=12$), some improvement needed (31% [95% CI: 25,37], $n=75$), and no improvement needed (59% [95% CI: 53,65], $n=143$).

Family-Reported Emotions

Exploratory factor analysis categorized family-reported emotions into seven categories: ambivalent, guilt and self-blame, worry about staying with the patient, burden about proxy judgment, burden to others, acceptance, helplessness, and relief. More than half of the respondents had ambivalent wishes, guilt and self-blame, and worries about staying with the patient. One-fourth to one-third reported that they felt a burden over proxy judgments, burden to others, acceptance, and helplessness. Less than 5% reported positive feelings such as relief (Table 2).

Family-Reported Patient Behavior

The bereaved family members reported various patient behaviors other than "psychiatric symptoms." More than half of the respondents reported that, during the delirium episodes, the patient expressed physiologic desires, seemed incoherent but talked about actual past events, and talked about uncompleted life tasks. In addition, about 30% said that the patient apologized

Table 2
Family-Reported Emotions

	Agree or Strongly Agree	95% CI	Factor Loadings	Alpha
	% (*n*)			
Ambivalent				N.C.
Simultaneously wanted the patient both to stay awake and to relieve the patient from suffering.	64 (155)	58,70	N.C.	
Simultaneously wanted the patient both to live longer and to die without suffering.	40 (97)	34,46	N.C.	
Guilt and self-blame				0.87
Could not understand what the patient wished for.	62 (149)	55,68	0.89	
Might not be able to realize the patient's unfulfilled wishes.	56 (135)	49,62	0.89	
Guilty, could not do enough for the patient.	52 (126)	46,58	0.88	
Worry about staying with the patient				0.77
Worried about caring the patient alone.	58 (140)	51,64	0.89	
Anxious about taking their eyes off the patient.	57 (139)	51,64	0.88	
Burden about proxy judgment				N.C.
Burden about having to make a decision on behalf of the patient.	39 (94)	33,45	0.86	
Burden to others				0.60
Distressed as the patient troubled others.	38 (91)	32,44	0.68	
Not wanting other members of the family to see the patient.	35 (84)	29,41	0.69	
Sad to see the patient having completely changed.	29 (71)	24,35	0.85	
Acceptance				N.C.
Just accepting the fact.	35 (84)	29,41	0.96	
Helplessness				0.78
Helplessness about what to do.	32 (78)	27,38	0.87	
Not sure about what was happening.	28 (68)	23,34	0.91	
Relief				0.81
Felt relieved.	3.3 (8)	2.0,6.0	0.89	
Felt happy.	2.5 (6)	1.0,5.0	0.91	

N.C. = not calculated.

for past events and was distressed as they noticed that they were talking strangely. About 20% of the family members reported a transcendent experience, that is, that the patient talked to or met people who had died (Table 3).

Family-Perceived Meaning of Delirium and Interpretation of the Causes of Delirium

About half of the respondents perceived delirium as a sign of approaching death, the patient trying to express what to say, or patient suffering. About one-fourth to one-third perceived delirium as a natural part of the dying process, dreaming, a transcendent phenomenon (entering the after-death world), or relief from actual suffering. Forty to 60% of the families interpreted the causes of delirium as pain/physical discomfort or medication effects (Table 4).

Family-Reported Professional Care Practice for Delirium

The families generally reported high adherence to the recommended care practice for terminal delirium. Eighty percent or more families agreed that professionals treated patients the same as before, tried to understand what the patient wanted to say, were sufficiently compassionate to the family, explained the expected course along with daily changes, and respected the patient's subjective world (Table 5).

Determinants of Family-Perceived Emotional Distress and Necessity of Improvement

Compared with the family members with low-level distress, family members with high-level distress were more likely to experience agitated behavior, incoherent speech, the patient talking about uncompleted life tasks, the patient appearing incoherent but talking about actual past events, and being distressed by noticing that they were talking strangely; more likely to interpret the causes of delirium as pain/physical discomfort, medication effects, psychosis/"getting crazy," and mental weakness/death anxiety; less likely to report

Table 3
Family-Reported Patient Behavior in the Delirium Episodes

	Occasionally	95% CI	Often	95% CI
	% (*n*)		% (*n*)	
"Psychiatric symptoms"				
Incoherent speech	53 (128)	47, 59	25 (60)	20, 31
Mentally clear in some situations within the day	36 (88)	31, 43	37 (89)	31, 43
Hallucinations	34 (83)	29, 41	17 (40)	12, 22
Agitated behavior	31 (75)	25, 37	15 (36)	11, 20
Other than "psychiatric symptoms"				
Expressed physiologic desires (excretion, thirst)	31 (76)	26, 38	40 (96)	34, 46
Seemed incoherent but talked about actual past events	41 (100)	35, 48	26 (62)	20, 32
Talked about uncompleted life tasks	32 (78)	27, 38	24 (57)	19, 29
Good mood	33 (80)	27, 39	7.4 (18)	5.0, 11
Apologized for past events	22 (53)	17, 28	6.6 (16)	4.0, 11
Distressed as the patient noticed him/herself talking strangely	21 (51)	16, 27	6.6 (16)	4.0, 11
Said that the patient talked to or met people who had died	18 (44)	14, 24	4.1 (10)	2.0, 7.0

the medical professionals as present with the family; and more likely to report the patient being physically restrained (Table 6).

Compared with the family members who perceived a low-level necessity of improvement, family members who perceived a high-level necessity of improvement were more likely to be young and male; more likely to interpret the causes of delirium as pain/physical discomfort and medication effects; less likely to report that the medical professionals were present with the family, respected the patient's subjective world, explained the expected course along with daily changes, tried to understand what the patient wanted to say, were sufficiently compassionate to the family, had facilitated communication before it became difficult, and had confirmed the patient's wishes before communication become difficult; and reported a lower score of the family care subscale of the Care Evaluation Scale.

Multiple logistic regression analyses revealed that the independent determinants of high-level distress or high-level necessity of improvement were younger age; male gender; experience of agitation and incoherent speech; interpretation of the causes of delirium as pain/

Table 4
Family-Perceived Meaning of Delirium and Interpretations About the Causes of Delirium

	Agree, or Strongly Agree	95% CI
	% (*n*)	
Meaning of delirium		
Sign of approaching death	59 (143)	53, 65
Trying to express what the patient wanted to do or say	52 (125)	45, 58
Suffering	45 (108)	38, 51
A natural part of the dying process	31 (74)	25, 37
Dream	25 (61)	20, 31
Entering after-death world	22 (54)	17, 28
Relief from actual suffering	22 (53)	17, 28
Happy and welcome experience	7.0 (17)	4.0, 11
Interpretation about the causes of delirium		
Pain or physical discomfort	60 (144)	53, 66
Medication effects	41 (99)	35, 47
Psychosis or "becoming crazy"	19 (46)	15, 24
Mental weakness or death anxiety	15 (37)	11, 20

Table 5
Family-Reported Professional Care Practice for Delirium

	Practiced	95% CI
	% (*n*)	
Treated patients the same as before	94 (227)	90, 96
Tried to understand what the patient wanted to say	88 (214)	84, 92
Was sufficiently compassionate to the family	86 (208)	81, 90
Explained the expected course along with daily changes	86 (207)	80, 89
Respected the patient's subjective world without denying "incoherent things"	83 (202)	78, 88
Discussed with the family about how to deal with the issue	75 (181)	69, 80
Explained the pathology of delirium (not dementia or psychosis)	72 (175)	66, 78
Was present with the family	71 (173)	65, 77
Facilitated with family members in communicating and being with the patient before it became difficult	68 (164)	62, 73
Explained the universality of delirium	66 (159)	59, 71
Confirmed the patient's wishes before communication became difficult	54 (131)	48, 60
Physical restraint		
Before admission to palliative care units	3.3 (8)	2.0, 6.0
In palliative care units	2.5 (6)	1.0, 5.0

physical discomfort, medication effects, or mental weakness/death anxiety; and medical staff being present with the family, respecting the patient's subjective world, explaining the expected course along with daily changes, and relieving the family care burden.

Discussion

This is, to our knowledge, the first systemic survey to investigate the potential correlations of the distress levels of families and the perceived necessity of improvement in care related to terminal delirium with family-reported professional care practice, family-reported patient behavior, and perception of the causes of delirium.

This survey revealed that, although a relatively small number of families (5.8%) reported that considerable or much improvement was necessary in the professional care they had received in certified palliative care units, about half of the families reported being very distressed or distressed about the experience of terminal delirium. This figure is relatively low compared with the previous two surveys,[6,7] but confirms that at least 50% of the families of patients with delirium experienced considerable emotional distress.

The most important finding of this study was the identification of factors associated with the distress levels of families and their perceived necessity of improvement. The chief factors included family experience of agitation, their interpretation of the causes of delirium, and their perception about the care they had received.

Consistent with previous surveys that identified agitation as a significant determinant of family distress,[6,7] family-reported agitation was an important determinant of family distress in this study. The control of agitation symptoms, therefore, is an important task for palliative care clinicians. This study revealed, however, that ambivalent wishes between symptom control and maintaining communication were the most common emotions of the families. Together with qualitative studies stressing the importance of ambivalent wishes in this situation,[12,14] clinicians should note that families want not only symptom palliation but also much broader elements of quality of life, such as maintaining cognitive control, communicating with others, and living as long as possible.[26,27] That is, clinically, pharmacologically sedative therapy should not be routinely applied to control agitation symptoms without careful individualized considerations, and the depth or duration of sedation should be closely adjusted for each situation.[28]

Families often interpreted delirium as the consequences of pain/physical discomfort, medication effects, psychosis/"becoming crazy," or mental weakness/death anxiety, and these interpretations were significantly associated with both family distress and necessity of improvement. These findings confirm the great importance of information focusing on the cause and pathologies of delirium (i.e., terminal delirium is usually not an expression of pain, medication effects, "becoming crazy," or mental weakness), as stated in expert literature.[10,14]

The major care practices related to a family's emotional distress and necessity of improvement included being present with the family, respecting the patient's subjective world, explaining the expected course with daily changes, and relieving the family care burden.

Of special note, as this study suggests, respecting the patient's subjective world can be an important care strategy in terminal delirium. This care strategy was associated with the overall necessity of improvement, and the family members experienced various patient behaviors other than "psychiatric symptoms": the patient expressed physiologic desires, seemed incoherent but talked about actual past events, talked about uncompleted life tasks, and apologized for past events. Consistent with the recommendations of palliative care textbooks,[8–11] these findings suggest that the care strategy for terminal delirium may include exploring and fulfilling unmet physiological needs behind delirium symptoms, and trying to understand the "strange" behavior of delirious patients as a potentially meaningful experience to find a clue for important landmark events and achieve uncompleted life tasks for patients and families.

Among care strategies investigated in this study, only being with the patient was associated with families' emotional distress. This result indicates, as nonempirical literature stresses the importance of "being" for palliative care clinicians,[8–11] being with the families of delirious patients is an essential element of care.

Table 6
Determinants of Family-Reported Emotional Distress and Necessity of Improvement

	Emotional Distress Level				Necessity of Improvement			
	Univariate Analyses		Multivariate Analysis[a]		Univariate Analyses		Multivariate Analysis[b]	
	High-Distress ($n=77$)	Low-Distress ($n=165$)	Odds Ratio [95% CI]	P	High Necessity ($n=89$)	Low Necessity ($n=143$)	Odds Ratio [95% CI]	P
Background								
Age (family)					55 ± 11	60 ± 14[c]	0.96 [0.93–0.99]	0.016
Sex (family, female)					64% ($n=57$)	79% ($n=113$)[c]	0.22 [0.096–0.50]	0.001
Sex (patient, female)					45% ($n=40$)	31% ($n=44$)[c]		
Family-reported patient behavior[d]								
Agitated behavior	0.85 ± 0.78	0.51 ± 0.69[e]	1.5 [0.98–2.4]	0.063				
Incoherent speech	1.2 ± 0.72	0.97 ± 0.64[f]	1.7 [1.0–2.9]	0.042				
Talked about uncompleted life tasks	1.0 ± 0.83	0.73 ± 0.77[f]						
Seemed incoherent but talked about actual past events	1.2 ± 0.72	0.90 ± 0.76[c]						
Distressed as the patient noticed	0.49 ± 0.73	0.30 ± 0.53[c]						
Interpretations of the causes[g]								
Pain or physical discomfort	3.0 ± 1.3	2.5 ± 1.2[f]	1.3 [0.95–1.7]	0.099	2.9 ± 1.2	2.5 ± 1.2[c]		
Medication effects	2.3 ± 1.2	2.0 ± 1.2[c]			2.4 ± 1.1	1.9 ± 1.200[f]	1.5 [1.1–2.1]	0.014
Mental weakness or death anxiety	1.6 ± 1.3	1.3 ± 0.94[c]	1.3 [0.97–1.8]	0.078				
Psychosis or "getting crazy"	1.6 ± 1.3	1.3 ± 1.1[c]						
Family-reported professional care[h]								
Was present with the family	62% ($n=48$)	76% ($n=125$)[c]	0.49 [0.23–1.0]	0.068	58% ($n=52$)	83% ($n=119$)[e]	0.35 [0.12–1.0]	0.053
Respected the patient's subjective world					81% ($n=72$)	88% ($n=126$)[c]	0.16 [0.019–1.3]	0.088
Explained the expected course					79% ($n=70$)	92% ($n=132$)[f]	0.13 [0.028–0.64]	0.011
Tried to understand what the patient said					87% ($n=77$)	93% ($n=133$)[e]		
Was sufficiently compassionate to the family					76% ($n=68$)	93% ($n=133$)[e]		
Had confirmed the patient's wishes before communication became difficult					44% ($n=39$)	64% ($n=91$)[e]		

(*Continued*)

Table 6 (Continued)

	Emotional Distress Level				Necessity of Improvement			
	Univariate Analyses		Multivariate Analysis[a]		Univariate Analyses		Multivariate Analysis[b]	
	High-Distress ($n = 77$)	Low-Distress ($n = 165$)	Odds Ratio [95% CI]	P	High Necessity ($n = 89$)	Low Necessity ($n = 143$)	Odds Ratio [95% CI]	P
Had facilitated communication before it became difficult					62% ($n = 55$)	73% ($n = 105$)[f]		
Relieved the family care burden[i]					6.4 ± 2.5	7.9 ± 2.5[e]	0.84 [0.73–0.98]	0.025
Physical restraint	10% ($n = 8$)	3.6% ($n = 6$)[c]						

[a] $R^2 = 0.15$.
[b] $R^2 = 0.37$.
[c] $P < 0.05$.
[d] Rated as 0 (none), 1 (occasionally), and 2 (often).
[e] $P < 0.001$.
[f] $P < 0.01$.
[g] Rated as 0 (strongly disagree) to 4 (strongly agree).
[h] Rated as practiced or not.
[i] Rated on the family care subscale of the Care Evaluation Questionnaire. Lower score indicates a family-perceived higher necessity of care to relieve the family care burden.

The family-perceived necessity of improvement in care to relieve the family care burden was a significant determinant in the overall family-perceived necessity of improvement. As the family is an important target in palliative care, clinicians should make maximum efforts to relieve the family care burden, through reassuring the families that they can leave the patients' care to the staff, making the hospital environment comfortable for the families, and coordinating support from other members of the family.

Of interest was that this study highlighted some specific emotions evoked by the experience of terminal delirium. In this study sample, the three major emotions were ambivalent wishes, guilt and self-blame, and worry about staying with the patient. As only a few qualitative studies proposed a care strategy to relieve such specific distress,[14] more empirical studies are needed to understand in-depth family emotions related to terminal delirium and explore a specific care strategy.

Despite several strengths, including the success in obtaining a large sample with more than a 70% response rate, this study has some limitations. First, due to its retrospective nature, there might be a recall bias. Second, some families denied the episode of delirium despite a psychiatrically confirmed diagnosis, and might recall episodes other than delirium. Third, as all patients received specialized palliative care, adherence levels to recommended care practice were generally high and might result in low-sensitivity statistical analyses, and the findings could not be automatically generalized to other situations. Fourth, the cross-sectional design of this study cannot allow the causality of the associations identified. Fifth, we excluded 6.7% of the potential respondents with profound emotional distress due to ethical reasons. Finally, what is important for a good death, such as maintaining consciousness and dying during sleep, is different among cultural backgrounds,[27,29] and the results might not be automatically applied to different cultural settings.

In conclusion, a considerable number of family members experienced high levels of emotional distress and felt some need for improvement of the care for terminal delirium. Control of agitation symptoms with careful consideration of ambivalent family wishes,

information about the pathophysiology of delirium, being present with the family, respecting the patient's subjective world, explaining the expected course with daily changes, and relieving the family care burden can be useful care strategies. Intervention trials to determine the efficacy of these care strategies are needed.

References

1. Bruera E, Miller J, McCallion J, et al. Cognitive failure in patients with terminal cancer. a prospective study. J Pain Symptom Manage 1992;7:192–195.

2. Lawlor PG, Ganon B, Mancini IL, et al. Occurrences, causes, and outcome of delirium in patients with advanced cancer. A prospective study. Arch Intern Med 2000;160:786–794.

3. Massie MJ, Holland J, Glass E. Delirium in terminally ill cancer patients. Am J Psychiatry 1983; 140:1048–1050.

4. Morita T, Tei Y, Tsunoda J, et al. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. J Pain Symptom Manage 2001;22:997–1006.

5. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 1997;79:835–842.

6. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouse/caregivers, and their nurses. Psychosomatics 2002;43:183–194.

7. Morita T, Hirai K, Sakaguchi Y, Tsuneto S, Shima Y. Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. Psychosomatics 2004;45(2):107–113.

8. Breitbart W, Jaramillo JR, Chochinov HM. Palliative and terminal care. In: Holland JC, Breitbart W, Jacobsen PB, Lederberg MS, eds. Psycho-oncology. New York: Oxford University Press, 1998: 437–449.

9. Casarett DJ, Inouye SK. Diagnosis and management of delirium near the end of life. Ann Intern Med 2001;135:32–40.

10. Kuebler KK, English N, Heidrich DE. Delirium, confusion, agitation, and restlessness. In: Ferrell BR, Coyle N, eds. Textbook of palliative nursing. New York: Oxford University Press, 2000: 290–308.

11. Shuster J. Delirium, confusion and agitation at the end-of-life. J Palliat Med 1998;1:177–185.

12. Susan B. The impact on the family of terminal restlessness and its management. Palliat Med 2003; 17:454–460.

13. Pierre G, Cecile C, Pierre A, et al. Delirium in advanced cancer: a psychoeducational intervention for family caregivers. J Palliat Care 2002;18(4): 253–261.

14. Nanba M, Morita T, Imura C, et al. Terminal delirium: a family's live experience. Palliat Med. In press.

15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association.

16. Morita T, Ikenaga M, Adachi I, et al. Family experience with palliative sedation therapy for terminally ill cancer patients. J Pain Symptom Manage 2004;28:557–565.

17. Morita T, Akechi T, Ikenaga M, et al. Communication about the ending of anticancer treatment and transition to palliative care. Ann Oncol 2004; 15:1551–1557.

18. Anetth G, Ingegerd BE, Dag L. Patients' experience of being critically ill or severely injured and cared for in an intensive care unit in relation to the ICU syndrome. Intensive Crit Care Nurs 1998;14:294–307.

19. Brigit R, Wendy C. Patients' dreams and unreal experiences following intensive care unit admission. Nurs Crit Care 2004;9(4):173–180.

20. Cynthia M, Sherill NC. Delirium: elders tell their stories and guide nursing practice. Medsurg Nurs 2003;12(5):318–323.

21. Edith MA, Ingalill RH, Astrid N, et al. The meaning of acute confusional state from the perspective of elderly patients. Int J Geriatr Psychiatry 2002;17:652–663.

22. Fagerberg I, Jonhagen ME. Temporary confusion: a fearful experience. J Psychiatr Ment Health Nurs 2002;9:339–346.

23. Irene S. A small exploratory study of the reaction of older people to an episode of delirium. J Adv Nurs 1997;25:942–952.

24. Morita T, Hirai K, Sakaguchi Y, et al. Measuring the quality of structure and process in end-of-life care from the bereaved family perspectives. J Pain Symptom Manage 2004;27:492–501.

25. Matsuoka Y, Miyake Y, Arakaki H, et al. Clinical utility and validation of the Japanese version of Memorial Delirium Assessment Scale in a psychogeriatric inpatient setting. Gen Hosp Psychiatry 2001;23: 36–40.

26. Steinhauser KE, Christakis NA, Clipp EC, et al. Factors considered important at the end of life by patients, family, physicians, and other care providers. JAMA 2000;284:2476–2482.

27. Hirai K, Miyashita M, Morita T, et al. Good death in Japanese cancer care: a qualitative study. J Pain Symptom Manage 2006;31:140–147.

28. Morita T, Bito S, Kurihara Y, Uchitomi Y. Development of a clinical guideline for palliative sedation therapy using the Delphi method. J Palliat Med 2005;8:716–729.

29. Fainsinger RL, Nunez-Olarte JM, Demoissac DM. The cultural differences in perceived value of disclosure and cognition: Spain and Canada. J Palliat Care 2003;19:43–48.

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Physician and Nurse Attitudes Toward Artificial Hydration for Terminally Ill Cancer Patients in Japan: Results of 2 Nationwide Surveys

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This study investigated physician and nurse attitudes toward artificial hydration in terminally ill cancer patients and compared differences in attitudes between these 2 professions and among clinical settings in Japan. The response rate was 53% (584/1123) for physicians and 79% for nurses (3328/4210). More physicians answered that artificial hydration alleviates the sensation of thirst. More palliative care unit physicians and nurses answered that withholding artificial hydration alleviated several physical symptoms. Oncologists answered that artificial hydration alleviated the sensation of thirst and fatigue. Discussion among patient-centered teams and individualized decision making are important. Because the differences identified here are attributable to differences in knowledge of artificial hydration for terminal cancer patients, oncologists should place greater emphasis on the opinion of palliative care specialists. Medical practitioners caring for terminal cancer patients should consider a broader range of views on hydration therapy, with a focus on effective hydration techniques and alternative interventions.

Keywords: palliative care; fluid therapy; attitude

Artificial hydration for terminally ill cancer patients is controversial.[1,2] Arguments usually focus on symptom control, such as fluid retention symptoms,[3] delirium,[4] nausea,[5] sensation of thirst,[6] the urination burden,[7] and ethical problems.[8-11]

In Japan, Morita et al[12] identified 3 factors that significantly correlated with the decision to provide artificial hydration: decision-makers who were less involved in end-of-life care, the belief that artificial hydration is effective for symptom palliation, and the belief that artificial hydration is a component of minimum standards of care. Despite reports of various negative effects, physicians who work in health centers other than palliative care units (PCUs) usually favor high-volume hydration.[12] In addition, a second article by Morita et al[13] on physician-reported and nurse-reported effects of artificial therapy on symptoms in terminally ill patients with cancer found that physicians and nurses in oncology and palliative care settings frequently observed that artificial hydration caused a deterioration in fluid retention symptoms, with limited benefit in alleviating symptoms of dehydration.[13]

The beliefs of physicians about artificial hydration significantly affect decision making by both patients and their families.[14,15] These findings highlight the importance of examining these beliefs in detail, yet attitudes toward artificial hydration have not been investigated in detail, especially for nurses.

The present report is based on 2 nationwide surveys conducted in Japan—the first in physicians[13] and

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the second in nurses—to clarify respective attitudes toward symptom control and ethical issues in artificial hydration in terminally ill cancer patients. Differences in attitudes were compared between professions and among clinical settings. The 2 surveys were conducted separately, but the clinical settings of the respondents were similar and the questions were identical.

Methods

Participants

The first questionnaire was part of a previous survey on physician attitudes toward terminal hydration, reported in detail elsewhere.[13] Participants were recruited from 2 nationwide organizations, the Japanese Association of Clinical Cancer Centers and the Japanese Association of Hospice and Palliative Care Units. The former included 28 centers of excellence in clinical oncology, and the latter, a wider range of 80 hospitals with PCUs or inpatient hospices. Of these, 16 cancer centers and 73 hospitals participated in the present study. These were augmented by a further 4 general hospitals and a palliative care clinic belonging to the Japan Palliative Oncology Study Group.

Representatives of each institution were asked to identify for potential participation attending physicians who specialized in the care of terminally ill cancer patients. A total of 1123 physicians were recruited as a heterogeneous sample of physicians working at cancer centers, general hospitals, and PCUs.

The second questionnaire was part of a previous survey conducted in October 2002. Participants were recruited in the same manner as for the physician survey. The participating institutions included 24 cancer centers and 55 hospitals belonging to the above 2 organizations as well as 4 general hospitals. Representatives of each institution were asked to identify for potential participation attending nurses working in units for the care of terminally ill cancer patients. A total of 4210 nurses were recruited as a heterogeneous sample of nurses working at cancer centers, general hospitals, and PCUs.

In Japan, the Ministry of Health, Labor and Welfare has strongly supported the expansion of specialized palliative care services. Coverage for PCUs under the National Medical Insurance began in 1991, and the number of PCUs has increased dramatically, from 5 that year to 135 in 2004. In contrast, the growth of home-based palliative care programs has been slow, and in fact, palliative care teams were not covered by National Medical Insurance until 2002. The most common type of specialized palliative care service in Japan is the PCU. We selected medical practitioners belonging to general wards of cancer centers, general hospitals, and PCUs as study targets for this investigation.

Questionnaire

The questionnaire (available from the authors) was developed by the Japan Palliative Oncology Study Group. Face validity of the questionnaire was confirmed by a pilot test with 11 physicians and 15 nurses from oncology and palliative care settings.

The respondents were first asked to report their backgrounds, including the number of years of clinical practice, practice setting, number of cancer deaths in their unit during the preceding year, and specialty (physicians only). The 2 questionnaires then made 15 identical statements developed after an extensive literature review of attitudes toward terminal artificial hydration, with a particular focus on symptom control and ethical issues.[9-11,14-21] The 15 statements were:

1. Artificial hydration alleviates sensations of thirst.
2. Artificial hydration alleviates fatigue.
3. Artificial hydration alleviates delirium.
4. Withholding artificial hydration alleviates the burden of urination.
5. Withholding artificial hydration alleviates nausea/vomiting.
6. Withholding artificial hydration alleviates cough/sputum/dyspnea.
7. Withholding artificial hydration leads to the loss of patient trust.
8. Withholding artificial hydration leads to the loss of family trust.
9. Withholding artificial hydration leads to undertreatment in compromised patients.
10. Withholding artificial hydration often shortens patient survival.
11. Withholding artificial hydration can be criticized by colleagues.
12. Artificial hydration is essential for meeting minimum standards of care.
13. Determining the medical indications for artificial hydration is difficult.
14. Patients have the right to refuse artificial hydration.
15. Maintaining a venous route is a burden on the patient.

Respondents were asked to evaluate each statement and respond using a 6-point Likert scale (strongly agree to strongly disagree).