

For euthanasia, 46–50% of the general population preferred this approach compared with 41% of the PCU-bereaved families. There was no significant difference in preference for euthanasia between groups ($P = 0.09$).

factors associated with preferences

place of end-of-life care. Summarized in Table 3. Respondents who preferred 'Home' were more likely to regard 'Dying in a favorite place', 'Maintaining hope and pleasure', 'Natural death' and 'Religious and spiritual comfort' as important for a good death than those who preferred 'Acute hospital' (reference category).

Respondents who preferred 'PCU' were more likely to regard 'Being respected as an individual' and 'Religious and spiritual comfort' as important for a good death than those who preferred 'Acute hospital' (reference category).

Respondents who preferred 'Acute hospital' were more likely to be older, and to regard 'Unawareness of death' and 'Pride and beauty' as important for a good death, than those who preferred 'Home' or 'PCU', respectively.

Respondents who preferred 'PCU' were more likely to agree with positive statements about the PCU, such as 'Supports patients in living with dignity', 'Provides care for families' and 'Alleviates pain'. By contrast, those who preferred 'Acute hospital' were more likely to consider the PCU as 'A place where patients are isolated from the community'. Other descriptions of the PCU, including 'Provides no medical treatments', 'A place where people only wait to die', 'Shortens the patient's life' or 'Expensive', were not significantly associated with a preference for 'PCU' (data not shown).

prognostic disclosure (1–2 month scenario). Summarized in Table 4. Respondents who preferred knowing their prognosis were more likely to regard 'Control over the future' as important for a good death, and less likely to regard 'Unawareness of death' as important, or to agree with the statement 'I could not cope if I was told my cancer was incurable'.

treatment for severe refractory physical distress. Summarized in Table 5. Respondents who preferred care without sedation were

Table 3. Factors associated with preference for place of end-of-life care

	Home			PCU		
	Odds ratio	95% CI		Odds ratio	95% CI	
Background of respondents						
Age (per decade)	0.77	0.67–0.89	***	0.76	0.65–0.88	***
Groups						
Nonbereaved general population/Bereaved general population	1.47	1.07–2.02	*	1.49	1.06–2.09	*
PCU bereaved families/Bereaved general population	1.39	0.76–2.56		4.62	2.58–8.26	***
Perceptions of PCUs^a						
Support patients in living with dignity	1.21	0.83–1.77		1.86	1.26–2.73	***
Provide care for families	1.57	1.08–2.28	*	2.60	1.77–3.80	***
Alleviate pain	1.28	0.91–1.82		1.72	1.21–2.46	**
Isolate patients from the community	0.98	0.70–1.38		0.67	0.47–0.95	*
Good death^b						
Dying in a favorite place	1.43	1.20–1.70	***	1.01	0.85–1.20	
Unawareness of death	0.75	0.63–0.89	**	0.82	0.68–0.98	*
Pride and beauty	0.76	0.63–0.93	**	0.69	0.57–0.84	***
Maintaining hope and pleasure	1.42	1.14–1.77	**	1.14	0.91–1.42	
Natural death	1.25	1.08–1.45	**	1.14	0.98–1.33	
Religious and spiritual comfort	1.16	1.05–1.29	**	1.16	1.04–1.29	**
Being respected as an individual	1.03	0.85–1.26		1.25	1.02–1.54	*
Good relationship with family	1.12	0.88–1.41		0.72	0.57–0.91	**
Cancer-related beliefs^c						
It is difficult for me to receive care at home in my home care environment	0.61	0.52–0.71	***	1.14	0.96–1.35	
Artificial hydration and nutrition should be continued as the minimum standard until death	0.82	0.69–0.98	*	0.77	0.64–0.92	**
Physicians are uncomfortable discussing death	1.21	1.02–1.44	*	1.05	0.88–1.26	
Max-rescaled R ² 0.36						

The dependent variable had three categories: acute hospital, home and PCU. The latter two were compared with the former (acute hospital category), which was omitted from the tables. Only outcomes found to have significant results in multivariate analysis are presented.

CI, Confidence interval; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

^aRated on a five-response category, and collapsed into: '1 (strongly agree) or 2 (agree)' and '3 (neither agree nor disagree), 4 (disagree), 5 (strongly disagree) or did not know'. The former was compared with the latter.

^bRated as the degree of importance of each statement from 1 (absolutely unnecessary) to 7 (absolutely necessary).

^cRated as the degree of agreement with each statement from 1 (strongly disagree) to 5 (strongly agree).

Table 4. Factors associated with preference for prognostic disclosure

	(Physician to inform me only if I ask)		(Physician to check me first whether I want to know)		(Physician to initiate discussion and inform me in detail)				
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI			
Background of respondents									
Age (per decade)	0.96	0.84–1.11	0.83	0.71–0.98	*	1.03	0.89–1.19		
Good death ^a									
Control over the future	1.45	1.26–1.67	***	2.96	2.46–3.56	***	3.35	2.83–3.95	***
Unawareness of death	0.70	0.58–0.83	***	0.48	0.39–0.59	***	0.43	0.36–0.52	***
Pride and beauty	0.95	0.79–1.14		0.82	0.67–1.01		0.78	0.64–0.94	**
Preparation for death	1.24	1.03–1.49	*	1.11	0.89–1.38		1.24	1.01–1.51	*
Cancer-related beliefs ^b									
I could not cope if I was told my cancer was incurable	0.70	0.60–0.82	***	0.53	0.44–0.64	***	0.38	0.32–0.45	***
Max-rescaled R ² 0.32									

The dependent variable had four categories: 'Not to discuss at all', 'Physician to inform me only if I ask', 'Physician to check me first whether I want to know', or 'Physician to initiate discussion and inform me in detail'. The last three were compared with the first category ('Not to discuss at all'), which was omitted from the tables. Only outcomes found to have significant results in multivariate analysis are presented.

CI, Confidential interval; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

^aRated as the degree of importance of each statement from 1 (absolutely unnecessary) to 7 (absolutely necessary).

^bRated as the degree of agreement with each statement from 1 (strongly disagree) to 5 (strongly agree).

more likely to regard 'Fighting against cancer', 'Physical and cognitive control' and 'Preparation for death' as important for a good death; they were less likely to regard 'Physical and psychological comfort', 'Not being a burden to others' and 'Unawareness of death' as important for a good death, or to have legal knowledge of the double-effect act.

Compared with other respondents, those who preferred palliative sedation therapy were older, more likely to regard 'Physical and psychological comfort' and 'Unawareness of death' as important for a good death, and to agree with the statements 'I could not cope if I was told my cancer was incurable' and 'Cancer pain is sufficiently relieved if adequately treated'.

Compared with other respondents, those who preferred euthanasia were older, more likely to regard 'Physical and psychological comfort', 'Control over the future', 'Not being a burden to others' and 'Unawareness of death' as important for a good death, and to agree with the statement 'Physicians are uncomfortable discussing death'. They were less likely to regard 'Fighting against cancer' as important for a good death or to agree that 'Cancer pain is sufficiently relieved if adequately treated', and more likely to have legal knowledge about euthanasia.

discussion

To our knowledge, this is the first population-based survey clarifying the association between end-of-life care preferences and good-death concepts.

In a scenario where participants had incurable cancer, no physical distress and needed assistance with daily activities, most preferred end-of-life care and death at home or in a PCU. Moreover, PCU-bereaved families were more likely to prefer PCUs than the general population. Thus, PCUs had made a favorable impression on the bereaved families. In Japan, the

proportions of cancer patients who died at home or at a PCU in 2003 were only 6% [35] and 4.4% (Hospice Palliative Care Japan, unpublished data), respectively.

In Japan, many people regard a home death as unrealizable, because of insufficiencies in the home-care system and concern about caregiver burden [5]. Thomas and colleagues [36] reported that patient's informal care resources, and their experiences of health and social services, shaped their preferences for place of end-of-life care. Consistent with these recent findings [5, 36], in our current study, respondents who believed that they could not receive in-home care were significantly more likely to prefer hospitals to home. Thus, our results highlight the need for regional palliative-care programs, including home systems [20] and local inpatient services, to create a network and to deliver end-of-life care according to the preferences of patients and families [37]. It is thus important in future studies to clarify what family caregivers regard as a burden and also what patients feel makes them a burden to others in their care settings.

Consistent with findings in Australia [7], approximately 50% of our respondents preferred negotiating with their physician concerning prognostic disclosure. Notably, the preference for prognostic disclosure was associated with the good-death concept (specifically 'Control over the future' and 'Unawareness of death'). This finding suggests that approximately 50% of patients desire some level of negotiation about communication of prognosis, and that some Japanese patients do not necessarily consider autonomy as the most relevant factor, preferring to entrust decisions to their physicians [13]. In addition, 'Unawareness of death' seems more important in Japan than in Western countries, so living as usual without a feeling of impending death could be a core factor for the Japanese concept of a good death [21]. Thus, Japanese clinicians should recognize that routine prognostic disclosure and encouraging self-determination might not

Table 5. Factors associated with preference for treatment for refractory severe physical distress

	Care without sedation		Palliative sedation therapy			Euthanasia			
	Odds ratio	95%CI	Odds ratio	95%CI		Odds ratio	95%CI		
Background of respondents									
Age (per decade)			1.23	1.1–1.36	***	1.15	1.04–1.27	**	
Groups									
Nonbereaved general populations/ bereaved general population						0.63	0.47–0.85	**	
PCU bereaved families/bereaved general population									
Good death^a									
Physical and psychological comfort	0.58	0.5–0.67	***	1.80	1.55–2.12	***	1.57	1.35–1.81	***
Control over the future						1.58	1.42–1.75	***	
Not being a burden to others	0.79	0.69–0.90	***			1.37	1.20–1.56	***	
Unawareness of death	0.80	0.72–0.89	***	1.18	1.05–1.32	**	1.27	1.13–1.43	***
Good relationship with medical staff				1.30	1.07–1.56	**			
Fighting against cancer	1.59	1.45–1.75	***			0.63	0.57–0.70	***	
Physical and cognitive control	1.41	1.23–1.63	***						
Preparation for death	1.26	1.13–1.41	***						
Role accomplishment and contributing to others						0.86	0.77–0.97	*	
Good relationship with family						0.84	0.72–0.99	*	
Religious and spiritual comfort						0.90	0.84–0.97	**	
Environmental comfort	0.86	0.75–1.00	*						
Dying in a favorite place				0.86	0.75–0.99	*			
Cancer-related beliefs^b									
Cancer pain is sufficiently relieved if adequately treated				1.20	1.06–1.36	**	0.84	0.75–0.94	**
I could not cope if I was told my cancer was incurable				1.24	1.11–1.40	***			
Physicians are uncomfortable discussing death						1.15	1.02–1.28	*	
Opioids shorten life						1.14	1.02–1.27	*	
Correct legal knowledge of care options									
Double-effect act	0.78	0.65–0.93	**						
Euthanasia						0.45	0.37–0.56	***	
Max-rescaled R ²	0.17			0.12		0.23			

Only outcomes founded to have significant results in multivariate analysis are presented.

CI, Confidential interval; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

^aRated as the degree of importance of each statement from 1 (absolutely unnecessary) to 7 (absolutely necessary).

^bRated as the degree of agreement with each statement from 1 (strongly disagree) to 5 (strongly agree).

always be desirable for all patients, and that the physician–patient discussion premised on imminent death and preparing concerns for the aftermath might undermine a good death for some patients. Clinicians, however, face the challenge of helping their patients to achieve a complete life while facing their own mortality at the same time. Thus, communication skills focusing on daily concerns and negotiating short-term goals with careful consideration of the patient's good death concepts are of importance.

When facing severe refractory suffering, most respondents preferred sedation, although some preferred care without sedation or euthanasia. Consistent with previous studies [11, 16, 38], those who wanted care without sedation were more likely to regard preservation of intellectual activities as important for quality of dying, whereas those who preferred euthanasia were more likely to value not being a burden, having

symptom control and control over the future. Thus, clinicians should identify good-death concepts and explore the best solution for individuals, particularly through discussions about balancing symptom control and degree of consciousness.

PCU-bereaved families were less likely to prefer euthanasia than the bereaved general population, suggesting that experience of good-quality palliative care influenced their preferences. Physicians should thus communicate empirical evidence of high success rates for pain control and legal issues to their patients.

Our study had several limitations. First, because respondents were not terminally ill, the results could not necessarily be extrapolated to cancer patients. The patient's perspective is important, but we did not survey cancer patients because questions regarding dying were considered too burdensome to such patients in Japan. We believe, however, that this study

provides a unique and valuable perspective because bereaved families who had experienced end-of-life care at home, in acute hospitals, and in specialized inpatient PCUs (the best available practices in Japan) provided useful suggestions, and the generalizability was supported by the fact that 40% of the participants in the general population had a chronic disease. Second, the response rate among the general population was low, although similar to the average for population-based surveys in Japan [5]. Thus, a response bias might exist. Moreover, a relatively long interval, such as 10 years, might cause a recall bias, although it yielded similar conclusions to a limit of 5 years; it could also be influenced by changes in medical services over this time period. Third, preferences might change [6, 39] if individuals experienced the situations explored in the scenarios; future studies should evaluate the decision-making process longitudinally.

In conclusion, our analysis revealed that PCU-bereaved families were more likely to prefer PCUs as a place of end-of-life care, and less likely to prefer euthanasia than the general population. The PCUs were well received by bereaved families, and experience of high-quality palliative care influenced their preferences. Systematic efforts to improve the availability of good-quality palliative care are needed. Moreover, end-of-life care preferences were associated with good-death concepts, highlighting the importance of identifying patients' general goals before discussing specific treatment choices, as recommended in the Education in Palliative and End-of-life Care curriculum [40]. We therefore recommend that health-care providers should identify not only patients' preferences for end-of-life care, but also their beliefs about a good death, which should help to improve the quality of the dying process.

appendix

end-of-life care preferences (in a scenario where you had incurable cancer)

(1) Place of end-of-life care and death

If you had a 1–2 month life expectancy and no physical distress, but needed care assistance in your daily activities, which place would you prefer, and as a place of death? (Three possible categories: 'Home', 'Acute hospital' or 'PCU'.)

(2) Prognostic disclosure

If you had a 6-month life expectancy, how would you prefer to initiate a discussion of prognosis; and if you had a life expectancy of 1–2 months? (Four possible categories: 'Not to discuss at all'; 'Physician to inform me only if I ask', 'Physician to check with me first whether I want to know' or 'Physician to initiate a discussion and inform me in detail'.)

(3) Treatment of severe refractory physical distress

If you had severe refractory distress, would you want the following treatment?

- (a) Treatment so that the patient keeps consciousness clear even if distress is not alleviated (care without sedation).

(On a four-point Likert-type scale, ranging from '1. Absolutely do not want' to '4. Strongly want'.)

- (b) Administration of sleeping drugs so that the patient feels no distress because of a reduction in patient consciousness' (palliative sedation therapy). (On a four-point Likert-type scale, ranging from '1. Absolutely do not want' to '4. Strongly want'.)
- (c) Administration of lethal medications' (euthanasia). (On a four-point Likert-type scale, ranging from '1. Absolutely do not want' to '4. Strongly want'.)

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Primary concerns of advanced cancer patients identified through the structured life review process: A qualitative study using a text mining technique

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ABSTRACT

Objective: This study aims to clarify characteristics of the contents of life review in reminiscence therapies in cancer patients by age, gender, and stage of disease.

Methods: Sixteen patients who were terminally ill and were receiving anticancer treatments participated in life review therapy. Patients reviewed their lives according to their developmental stage, and they mainly reviewed impressive achievements. A clinical psychologist interviewed each patient four times and the total number of sessions was 64. The contents of each life review were transcribed, and a correspondence analysis and a significance test were conducted on these data to choose characteristic words or phrases.

Results: The main concern of 40-year-olds was "about children." For 50-year-olds, it was "how to confront death" and for 60-year-olds, "death-related anxiety" and "new discoveries". For 70-year-olds, "resignation about death" and "evaluative reminiscence of their lives" were most important, and for 80-year-olds the main concern was "relationships with others." When analyzing the data according to disease stage and gender, "transcendence to children", "reflection on their past behavior", and "gratitude for my family" were characteristic words for males receiving treatment, "work," "worries about children," "side effects," "homecare," and "reflection on their past behavior" were characteristic words for females receiving treatment. "Physical condition", "desire for death" and "how to confront death" were common phrases for males in the terminal stages of the disease process, while "resignation to life" was characteristic reaction for females.

Significance of results: There appear to be considerable differences in the focus of life review interviews by age, disease age, disease stage, and gender. Clinicians should consider these differences when using life-review therapy in order to tailor it to the individual.

KEYWORDS: Life review, Death and dying, Age, Disease stage, Gender

INTRODUCTION

Patients often review their disease history or their lives in nursing or care situations. Many studies on

reminiscence therapy have been conducted for the elderly in which they review their lives (Butler, 1974; Haight, 1988; Haight et al., 1995). These studies are mainly of three types (Thornton & Brotchie, 1987). The first are studies about the effects of reminiscence therapy, which demonstrate effects on depression (Haight et al., 2000), self-esteem (Haight et al., 1998), and life satisfaction (Haight, 1988).

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The second are interview studies such as the function of reminiscence therapy (Wong & Watt, 1991) or contents analysis; the third consists of the data from questionnaires (Webster, 1993). The present study is about contents analysis concerning the method of life review, which is included in the second category.

Structured life review is the most popular method in which reviewers look back at their lives along developmental stages similar to those outlined by Erikson (Haight, 1988). The other method is the autobiographical method (de Vries et al., 1995), in which reviewers write about a particular theme, for example, "love" or "family." They then talk their life experience of these themes in groups. Reminiscence therapy has three kinds of functions (Coleman, 1974). First is "simple reminiscence," in which the elderly review only their good memories. The second is "informative reminiscence," in which the elderly talk about their precious or formative experience from past experiences; and the third is "life review," in which the elderly review and evaluate their lives or an individual basis. The functions of reminiscence therapy have been categorized in more detail by Wong & Watt (1991).

Although patients often review their lives in nursing or care situations, relatively few studies on reminiscence therapy are available. Pickrel (1989) suggested that the effects of this therapy may hold possibility for cancer patients, and Wholihan (1992) demonstrated how various tools like photographs could be used to promote reminiscence therapy. Ando et al. (2006a) showed the effects of this therapy on depression and self-esteem, and Ando et al. (2007) demonstrated the effects of this therapy on quality of life for cancer patients. Moreover, Chochinov et al. (2005) demonstrated the effects of patients' life review, although the term "reminiscence therapy" was not used in this study. However, few studies consider the most appropriate methods for this therapy in cancer patients, and their emotional states are likely to differ depending upon their ages, gender, and stages of the disease. To promote reminiscence therapy methods and tailor them to individual cancer patients, we investigated differences in reminiscence therapy by choosing characteristic words and phrases in interviews from the viewpoint of age, gender, and disease stages in patients receiving anticancer treatments and those in the terminal stage of the illness.

METHODS

Subjects

The study included 4 cancer patients (1 man, 3 women) who were undergoing radiation treatment

or chemotherapy in a general hospital and 12 cancer patients (2 men, 10 women) with incurable cancer receiving specialized inpatient palliative care in the same region. The inclusion criteria for this study were (1) the patient had cancer, (2) the patient had no cognitive impairment, (3) the patient was 20 years of age or older, and (4) the primary physicians agreed that the patient would benefit from the psychological intervention of reminiscence therapy. The patients' ages ranged from 43 to 82 years, with a mean of 64. The primary tumor sites were breast ($n = 5$), liver ($n = 2$), colon ($n = 2$), lung ($n = 2$), thyroid ($n = 1$), stomach ($n = 1$), gallbladder ($n = 1$), uterus ($n = 1$), and prostate ($n = 1$).

Procedure

Ethical aspects of this study were validated by both the board and the ethical committee of two hospitals. An interviewer was a clinical psychologist. The interview procedure entailed a structured life review interview in which patients reviewed their childhood, adolescence, adult life, and current situation. Some of the questions asked were as follows: (1) Please tell me about your childhood. (2) Which events do you remember as being most impressive during your childhood? (3) How do you feel now when you review those impressive events? Four sessions were planned for each patient. Interviews were conducted in the dayroom or at the bedside. The contents of the patient's life review were recorded by the interviewer in the form of notes taken during or immediately after the session.

Analysis

Text mining is used to extract specific information from a large amount of textual data. We used Word Miner (Japan Information Processing Service, 2003). For example, when a company requires information on their customers' opinions, questions such as "What are the major concerns?" or "Who wants what?" are asked in a questionnaire. The responses are collected in the form of sentences, which are used as the raw data for text mining. Text mining involves three processes: feature extract (word segmentation and categorization or other functions to enter into the next process), the mining process (clustering or association by cluster analysis or correspondence analysis), and visualization (graphs or tables). A test was conducted such that the ratio of appearance frequency of fragments in the category (e.g., 40-year-olds group) versus all categories (e.g., all ages group). Morohoshi et al. (1999) demonstrated the efficacy of text mining in a consumers survey exploring their preference. We used text mining to obtain meaningful words when categorizing the

contents of each interview by age, stage of disease, and gender.

In the first process of text mining, characteristic extraction was performed, that is, the words in each sentence were separated. Words that had the same meaning were counted as the same word, for example, both "mom" and "mother" were counted as "mother." Moreover, articles or punctuation marks were deleted, leaving only meaningful words. These words are called "fragments." Text mining elicited 118 fragments, which were then subjected to correspondence analysis for chosen effective characteristics. In the present study, we conducted correspondence analysis on fragments pertaining to age, gender, and disease stages. In the final process of text mining, the results were presented in the form of tables and graphs.

RESULTS

From correspondence analysis between fragments and age, three components were chosen. Accumulative contribution ratio was 81.64%, and it shows the usefulness of this analysis. A test to choose significant (effective) words or phrases was conducted after correspondence analysis (Ohsumi, 2006), after which, the highest and lowest ranking words or phrases in a category were chosen (Table 1). The highest ranking fragments in the words of 40-year-olds represented concerns regarding children such as "My children are my emotional mainstay," "I hang on for my children," and "My children cannot accept my disease." These were chosen as the most influential words for this group of patients.

In the words of 50-year-olds, practical matters such as "I put things in order (concerns about aftermath)" and "I recovered from the shock" or willingness to confront death such as "I do not want to prolong my life" or "I want to die without suffering" were more commonly expressed.

Among 60-year-olds, words or phrases relating to spiritual pain such as "I desire to receive euthanasia," "I hate to be a burden to others," or "I want to live longer" were chosen. In addition, reflections on their behavior such as "I understand others' sufferings" or "I was an inconsiderate person" were also chosen.

In the words of 70-year-olds, mortality of death such as "Everyone passes the road to death" and "Let things take their course," or new discoveries such as "I have hurt others' feelings" and "I was an inconsiderate person" were observed. Moreover, evaluative words referring to the past such as "I have good memories of my mother" or "I enjoyed volunteer activities" were indicated more often than in the other age group.

In 80-year-olds, words showing dependence on others such as "I am influenced by my children," "Doctors help me," and "My children are kind to me" were chosen.

In the next analysis, following correspondence analysis and significance testing between fragments and the combination of gender and disease stages, two components were chosen and accumulative contribution ratio was 70.82%, which shows the usefulness of this analysis. High and low ranking words and phrases were chosen (Table 2).

For men receiving anticancer treatments, phrases emphasizing traditional concerns such as "I want to teach to my children" were the most influential words used by interviewees together with their rediscoveries of family values such as "I am grateful to my family," and "I share a strong family bond." For females receiving treatment, worries about children such as "My children cannot accept my disease," and "My children are my emotional mainstay" were characteristic words. Moreover, words related with daily life such as "I enjoyed my work," "I enjoyed volunteer activities," "I suffer from side effects," "I am glad to be able to eat a meal," or "I am anxious about home care" were their main concern.

For males in the terminal stage, words about how to confront death such as "I put things in order (preparing for death)," physical condition such as "I feel good," or adaptive wishes such as "I want to be away overnight" were chosen. For females in the terminal stages of cancer, words of resignation such as "Let things take their course" or "Everyone passes the road to death" were chosen together with words about human relationships such as "My family share good relationships."

DISCUSSION

Our analysis of the data shows that there are differences among characteristic words at each age. Patients in the 40-year-old group were mainly interested in children. Many words regarding children were related to worries about the future. It may be common in other countries that parents suffer when they cannot perform their parental role, but in addition, in Japanese culture, there is also a strong desire that people should not be a burden to others (Morita et al., 2004), despite being a family member.

Similar to the problems of a being a burden, telling the truth or talking about death with family members seem to be difficult because both patients and family think that they should not be a burden to each other, but, sometimes, patients are lonely because they cannot talk about death-related anxiety. This mechanics may be based on Japanese spirit (Kitayama, 1999). Clinicians should help patients and family members

Table 1. Words or Phrases which were selected by correspond analysis and significant test by ages

Order	40 years old		50 years old		60 years old		70 years old		80 years old	
	Significant fragments	value	Significant fragments	value	Significant fragments	value	Significant fragments	value	Significant fragments	value
No. 1	I enjoyed my work.	3.08	I put things in order.	2.95	The romantic relationships were not good.	2.96	I feel good.	2.89	I am influenced by my children.	2.65
No. 2	I want to teach to my children.	2.71	I want to be away overnight.	2.95	I desire to receive euthanasia.	2.21	I was an inconsiderate person.	2.89	Doctors help me.	2.65
No. 3	I hang on for my children.	2.71	My physical condition is good.	2.41	I am dissatisfied with previous treatments.	2.21	Everyone passes the road to death.	2.46	My parents were kind and tender.	2.27
No. 4	My children are my emotional mainstay.	2.31	I did not expect to get cancer.	1.74	I was dying once.	2.21	Let things take their course.	1.97	I share good relations with my family.	2.01
No. 5	My children cannot accept my disease.	2.31	I experienced a lonely childhood.	1.74	I was an inconsiderate person.	2.21	I enjoyed volunteer activities.	1.97	My physical condition is good.	2.01
No. 6	I regret delayed discovery of cancer.	2.31	I recovered from shock.	1.74	I hate to be a burden to others.	2.21	I have lived with my family's support.	1.97	I feel good.	1.23
No. 7	I share good relations with my brothers.	1.84	I like pets.	1.74	I understand others' sufferings.	2.21	I have hurt others' feelings.	1.97	I underwent rehabilitation.	1.15
No. 8	I am anxious about home care.	1.84	I do not want to prolong my life.	1.74	I am dissatisfied with my life.	2.21	I recognized after I got cancer.	1.97	I share bad relations with my family.	1.15
No. 9	My child believes that I will recover from cancer.	1.84	I value nature's beauty.	1.74	There is no value to life.	2.21	I have good memories of my mother.	1.93	I share good relations with my family.	1.15
No. 10	My medication causes mood swings.	1.84	I want to go home.	1.74	I regret the delayed discovery of cancer.	2.21	I have experienced the peaceful death of family members.	1.38	My children are kind to me.	1.15
No. 11	I am concerned for my family.	1.26	I want to die without suffering.	1.74	I could not believe that I had cancer.	2.21	I believe more in destiny than luck.	1.38	I want to continue my hobbies.	1.15
No. 12	I am grateful to my family.	1.26	Last moments' worries have been resolved.	1.74	I cannot move freely.	2.15	I quit my work after marriage.	1.38	I want to walk.	1.15
No. 13	I share a strong family bond.	1.26	I will not be able to move freely.	1.74	There were no explanations for treatments before.	1.78	I have hung on until now.	1.38	My family vests me at the hospital.	0.91
No. 14	I took care of my family.	1.26	I wonder if I should resolve old problems.	1.74	My physical condition is bad.	1.78	I am resting in a hospital now.	1.38	I enjoyed my hobbies.	0.57
No. 15	I liked taking care of my brothers.	1.26	I am not happy to die now.	1.74	I want to live longer.	0.77	I enjoyed conversations with others.	1.38	I have good memories of my mother.	0.57

Table 2. Characteristic words or phrases selected by correspondent analysis and significance test

Rank	anticancer treatments		anticancer treatments		terminal		terminal	
	males	value	females	value	males	value	females	value
No.1	I want to teach to my children.	4.19	I enjoyed my work.	2.95	I put things in order.	3.21	I enjoyed my hobbies.	2.45
No.2	I hang on for my children.	2.29	I was an inconsiderate person.	2.59	I want to be away overnight.	3.21	My family share good relationships	2.06
No.3	I am grateful to my family.	2.25	My children are my emotional mainstay.	2.2	I feel good.	2.63	My physical condition was bad.	2.06
No.4	I share a strong family bond.	2.25	My children can not accept my disease.	2.2	I coul not believe that I had cancer.	1.93	Everyone pass the road to death.	2.06
No.5	I was an inconsiderate person.	2.25	I regret delayed discovery of cancer.	2.2	I experienced a lonely childhood.	1.93	Let thing takes their course.	1.62
No.6	My turning point is at job change.	2.25	I enjoyed volunteer activities.	1.74	I recovered from shock.	1.93	There were no explanations for treatments before.	1.62
No.7	I have sweet memories of my childhood.	2.25	I share good relations with my brothers.	1.74	I do not want to prolong my life.	1.93	I have lived with my family's suport.	1.62
No.8	I enjoyed trips.	2.25	I am anxious about home care.	1.74	I value nature's beauty.	1.93	My parents were kinds to me.	1.62
No.9	I understand other's sufferings.	1.83	My child believes that I will recover from cancer.	1.74	I want to go home.	1.93	My physical condition was bad.	1.46
No.10	I can not move freely.	1.57	My mdedication causees mood swing.	1.74	I want to die without sufferings.	1.93	The romantic relationships were not good.	1.62
No.11	I began to consider others.	0.92	I am glad to be able to eat a meal.	1.74	Last moments' worries have been resolved.	1.93	I feel good.	1.46
No.12	I want to do something for my family.	0.8	I have hurt others' feelings.	1.74	I will not be able to move freely.	1.93	I want to live longer.	1.08
No.13	I think about enjoyments.	0.8	I recognized after I got illness.	1.74	I wonder if I should resolve old problems.	1.93	I like pets.	1.08
No.14	I worry about cancer recurrence.	0.8	I feel good.	1.63	I am not happy to die now.	1.93	I desire for eusanasia.	1.08
No.15	I am dissatisfied with my life.	0.8	I suffer from side effects.	1.63	I want to live longer.	1.46	I am dissatisfied with previous treatments.	1.08

to tell their emotion or intention redundantly to release their burdens.

Patients in the 50- and 60-year-old groups were more likely to be preoccupied by death-related anxiety about how they would confront the immi-nence of their own death. They may not expect to be cured of cancer, and they seem to try to prepare for death while reconstructing their lives to include the reality of their disease. Clinicians should therefore sympathetically help patients to find realistic solu-tions to these problems and develop coping strat-egies during the life review process. Moreover, to the sufferings such as "I desire to receive euthanasia" or "There is no value to life," "Psychotherapeutic In-tervention" by Breitbart et al. (2004) or "Meaning Making Intervention" by Lee et al. (2006), which focus on meaning of life or spirituality, may help patients. These focused interventions to these prob-lems may be more needed in addition to life review interview in Japan.

Patients in the 70-year-old group talked about their resignation to death. They also reviewed and evaluated their lives in detail, and with great ease, suggesting that this may be a more normative pro-cess for them. It is considered that some people may not survive until they turn 70, and thus, they are more likely to think of their own death, believing that they might not live much longer after this age. This shows that life review was more suitable for this age group in this research.

For patients in the 80-year-old group, profound life review with evaluation is sometimes more difficult, as this group tends to forget various things and retain only the most impressive memories they had. They did not talk so much about children or spiritual pain. These patients part with various memories and often accept their mortality. One 80-year-old woman said, "I have forgotten most of them. Old times seem good but I do not remember them." For these people, structured life reviews with evaluation is sometimes not suitable, and simple reminiscence therapy (Coleman, 1974), in which a person reviews his or her good memories without deep evaluation, may be more suitable.

Next, we investigated the results of fragments sep-arated into a combination between disease stage (anticancer treatment, terminal) and gender. Both men and women receiving treatment demonstrated reflection on their lives and new discoveries. Some patients had a renewed sense of gratitude to their family or reflected on their past behavior toward oth-ers. Illness had given them an opportunity to reflect upon their lives. From the viewpoint of a cultural as-pect, Kubler-Ross (1969) described the psychological stage as "Transaction with God"; however, in Japanese culture, it is thought of as "Consideration

for others" because consciousness of sin in the sight to God means very little to the Japanese, whereas harmony with others is the most important attitude they value. The clinician should help patients reeval-uate their human relations or make good ones new.

The theme of children was common among men and women receiving anticancer treatments. Women were worried about their children and whether they understood their disease, whereas men hoped to pass on their values to their children. Generativity may have been stronger in men, who wanted to pass their values on to their chil-dren and were newly grateful to their family or rea-lized their family bond, which they did not feel until they became ill. It may be, therefore, that illness provides Japanese men with a renewed appreciation of family and family life and a stronger desire to shape the values and future of their offspring.

In the terminal stage, men spoke in detail about confronting death, saying things like "I do not want to prolong death" or "I want to die without suffering." In contrast, women in this study showed interest in human relationships or resignation toward death. These suggest that the provision of information on how to confront death or a coping mechanism such as Lazarus and Folkman's (1988) may help reduce men's anxiety, whereas empathetic support for patients' voice about mortality will help women. Some patients said things such as "Everyone passes the road to death, I am very peaceful because I can meet my dead mother or dead old people in the hea-ven." Like these patients who believe in another world after death, Japanese often do not have a specific religion, but they seem to be more religious.

Comparison of words between those receiving an-ticancer treatments and those in the terminal stage of cancer showed that interests of patients receiving anticancer patients focused on treatments such as side effects, home care, treatments, or meals, whereas, in the terminal stage, interest seems to be focused more on value of human relationships, how to prepare for death, and resignation to their own mortality. These differences show the importance of many kinds of support, such as instrumental or emotional support, and clinicians need to prepare to talk about various ranges of interests.

Study Limitations and Conclusions

There are some limitations of the study, which was conducted in only two hospitals. Thus, it is difficult to generalize these results. Moreover, there are differences in the number of participants between men and women, the number of men being small. This is no surprise, however, because men do not like to talk about themselves in comparison to women

and refused to participate. Only a small number of patients met the criteria for entry to the study. In future research, we will examine these problems. However, although there are some limitations, the present study reinforced the need to carefully consider differing interests among ages, gender, and stages. Further study will be needed into the use of reminiscence therapy and the impact of variables in the appropriateness of different reminiscence techniques; but in general, the data presented here contain several developmental theories of aging and preparatory grief work.

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Efficacy, Safety, and Cost Effectiveness of Intravenous Midazolam and Flunitrazepam for Primary Insomnia in Terminally Ill Patients with Cancer: A Retrospective Multicenter Audit Study

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ABSTRACT

Background: Although intravenous midazolam and flunitrazepam are frequently administered for primary insomnia in Japan, there is no empirical study on their efficacy and safety.

Design and subjects: To compare the efficacy, safety, and cost-effectiveness of midazolam and flunitrazepam, a multicenter retrospective audit study was performed on 104 and 59 patients receiving midazolam and flunitrazepam, respectively, from 18 certified palliative care units.

Results: Median administration periods were 6 days and 9 days for midazolam and flunitrazepam, respectively. 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 efficacy (91% in the midazolam group versus 81% in the flunitrazepam group, $p = 0.084$), hangover effect (34% versus 19%, $p = 0.094$), delirium at night (12% versus 10%, $p = 1.0$) and delirium next morning (11% versus 15%, $p = 0.33$), treatment withdrawal (4.8% versus 1.7%, $p = 0.41$), and treatment-related death (0% versus 0%, $p = 1.0$). Flunitrazepam caused respiratory depression defined as physician or nurses records such as apnea, respiratory arrest, decreased respiratory rate, and respiratory depression significantly more frequently than midazolam (17% versus 3.8%, $p = 0.0073$). The maximum dose was more highly correlated with the administration period in the midazolam group than in the flunitrazepam group ($\rho = 0.52$, versus $\rho = 0.39$), and, for patients treated for 14 days or longer, the daily escalation dose ratio required for maintaining adequate sleep was significantly higher in the midazolam group than in the flunitrazepam group (11% versus 2.6%, $p = 0.015$). The costs of the initial and maximum administration were significantly higher in the midazolam group than in the flunitrazepam group ($p < 0.001$).

Conclusion: Intravenous midazolam and flunitrazepam appeared to be almost equal about efficacy and safety for primary insomnia, but flunitrazepam is less expensive and shows lower risk of tolerance development. A future prospective comparison study is necessary.

INTRODUCTION

INSOMNIA IS A COMMON and highly distressing symptom in cancer patients¹⁻³ and a large proportion of terminally ill cancer patients receive hypnotics.^{4,5} Al-

though a considerable number of patients with cancer cannot take medications orally because of dysphagia or intestinal obstruction, there have been few empirical reports about treatment approaches when oral administration of a hypnotic drug becomes difficult. In

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Japan, the benzodiazepines used in parenteral routes are midazolam, flunitrazepam, and diazepam.

When the oral use of hypnotic medications becomes difficult with the progression of the underlying disease, neither intravenous bolus doses nor subcutaneous infusion but an intravenous drip of midazolam or flunitrazepam dissolved in 100 mL normal saline is traditionally administered in Japanese palliative care units. In our previous nationwide survey,⁶ intravenous midazolam for insomnia was used in 89 institutions (79%) and intravenous flunitrazepam for insomnia in 59 institutions (53%). Western literature⁷ reports that the subcutaneous route is the most preferred route of choice for the palliative care population. In Japan, as well as some other countries,⁸⁻⁹ however, the majority of patients and families in palliative care units prefer the intravenous route, which is therefore frequently used to administer hypnotics in Japan.

On the other hand, benzodiazepines are often used to palliate serious symptoms refractory to standard palliative care, such as agitated delirium, dyspnea, pain and seizures in addition to procedural sedation.¹⁰⁻¹⁸ Midazolam has a favorable therapeutic profile in palliative care settings, including a short half-life, no active metabolites, water soluble, and available intravenously or subcutaneously.

On the other hand, few empirical studies have demonstrated the treatment effects of parenteral flunitrazepam.^{10,11} Subcutaneous flunitrazepam is not recommended because of skin irritation, and may have hangover effects resulting from its longer half-life. One of the problems in using intravenous benzodiazepines is complications such as a hangover effect¹⁹ (residual sleepiness and impairment of psychomotor and cognitive functioning during the day), delirium, and respiratory depression.²⁰ Prevention of the hangover effect and delirium is important, because clear consciousness is generally desired in the terminal stage²¹⁻²³ and respiratory effects resulting in unexpected death may increase when patients are elderly or weak.

In addition, tolerance related to the long-term administration of midazolam was reported in palliative care^{14-15,20,24} and intensive care units.²⁵⁻²⁷ In contrast, there is little information about tolerance to flunitrazepam.

To date, there has been no report of treatment when the oral use of hypnotics is difficult. A comparison of oral midazolam with oral flunitrazepam for preoperative medication²⁸ and insomnia²⁹ has been reported; however, there has been no report comparing the evaluation of these two intravenous benzodiazepines. Before conducting a prospective study, we performed a

retrospective chart review to compare the usefulness of these intravenous benzodiazepines for insomnia.

The aims of this multicenter study were therefore to compare the efficacy, safety, and cost effectiveness of these intravenous benzodiazepines in terminally ill cancer patients with primary insomnia.

PATIENTS AND METHODS

This is a retrospective preliminary study for subsequent prospective audit multicenter trials.

Patients

Eighteen certified palliative care units participated in this study.

In all institutions, we enrolled consecutive terminally ill patients with cancer who received an intravenous infusion of midazolam or flunitrazepam via a peripheral or central vein for primary insomnia before July 2005. Primary insomnia was defined as sleeplessness not attributable to a medical, psychiatric, or environmental cause by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. Indications other than primary insomnia, such as delirium and sedation for refractory symptoms such as dyspnea and pain, were excluded. We requested the enrollment of at most 10 consecutive patients in each institution because of large variations in the number of patients who received midazolam and flunitrazepam.⁶

Methods

This is a multicenter retrospective study based on chart review. In each institution, representative physicians completed the chart review using a structured data-collecting sheet designed for this study. The background data obtained included patient characteristics (age, gender, and primary site), other medications for insomnia, the duration from initial administration to death, the administration period, initial and maximum doses of midazolam or flunitrazepam, the administration method and cost. The cost was defined as market drug cost per day.

Measurements

Because of a lack of validated measurement tools, we evaluated efficacy and safety using ad hoc criteria on the day of initial administration (Appendix A). We designed evaluation methods to strictly follow the actual chart descriptions to minimize bias from retro-

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 \pm 13	65 \pm 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

^aRange 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% ($n = 20$)	

^aRange in brackets.

^bMaximum parenteral midazolam equivalent ≥ 20 mg/night

^cDue to a missing value, 103 patients were analyzed.

^dHypnotic escalation index % = percentage daily increase of initial dose = [(maximal doses–initial dose)/initial dose]/administration period $\times 100$.

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			0.094
Hangover	34% (n = 35)	19% (n = 11)	
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 equivalent³⁰ 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			p	Flunitrazepam group n = 59			p
	Continuous infusion all night n = 73	Infusion for one or two hours n = 22	Infusion until the patient fell asleep n = 9		Continuous infusion all night n = 14	Infusion for one or two hours n = 25	Infusion until the patient fell asleep n = 20	
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 mi-

dazolam 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 \geq 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

^aMaximum parenteral midazolam equivalent \geq 20 mg/night

^bHypnotic escalation index % = percentage daily increase of initial dose = [(maximal doses - initial dose)/initial dose]/administration period \times 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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