Family members were asked to rate their level of agreement with each of the 13 statements using a 5-point Likert-type scale with scores raging from 1 (disagree) to 5 (strongly agree).

We also collected background data. In addition, to confirm that the family had recognized delirium in the patient, we asked respondents whether they thought that the patient had delirium. We then excluded the responders of families who reported that they did not recognize the patient had delirium.

Statistical analysis

We described data distribution and calculated the 95% confidence intervals (CIs).

Results

Questionnaires were mailed to 235 bereaved family members, and 16 were returned as undeliverable. Responses were obtained from 169 bereaved family members (response rate 77%, 169/219). Of these, 22 were excluded because of missing data and 34 families reported they did not recognize the patient had delirium. Thus, all further analyses were performed on 113 responses. Table 2 summarizes the background of the patients and bereaved family members.

The family-reported usefulness of the leaflet about delirium was as follows: very useful, 33% (95% CI: 25–42; $n=37$); useful, 50% (40–59; $n=56$); slightly useful, 15% (10–23; $n=17$); and not useful, 2.7% (1–8; $n=3$). Date on family-reported experiences of usefulness of the leaflet about delirium can be seen in Table 1. With respect to the leaflet, more than 70% of respondents reported that they strongly agreed or agreed with: "helped me understand the dying process"; "helped me identify what I could do for the patient"; "helped me understand the symptoms and why changes occur"; "helped me understand the patient's physical condition"; and "was useful in preparing for the patient's death."

Discussion

To our knowledge, the present study is the first multicenter survey to investigate the family-perceived usefulness of a leaflet specifically designed to help family members of terminally ill cancer patients with delirium.

TABLE 2. BACKGROUND CHARACTERISTICS OF THE FAMILIES

	N	%
Patients		
Mean age (SD, years)	74 (10)	
Sex (male)	69	61
Bereaved families		
Mean age (SD, years)	57 (12)	
Sex (male)	31	27
Relationship to patient		
Spouse	47	42
Child	41	36
Parent	6	5.4
Sibling	2	1.8
Other	15	7.2
Mean interval from patient's death until survey (SD, median, months)	9.6 (3.5, 9.0)	

Percentages do not add up to 100% because of missing data.
Total responses analyzed = 113.
SD, standard deviation.

The important finding of this study is the family-reported high levels of usefulness of the leaflet. Of the bereaved families surveyed, 81% reported that they felt that the leaflet was "very useful" or "useful." The domains in which the leaflet intervention was perceived as being particularly useful were: "helped them understand the dying process"; "helped them identify what they could do for the patient"; "helped them understand the symptoms and why changes occur"; "helped them understand the patient's physical condition"; and "was useful in preparing for the patient's death." Thus, the leaflet could help the family members cope with this difficult situation by: (1) providing them with accurate information about delirium, especially the nature of the dying process and delirium, and why these changes occur; and (2) coaching them in terms of what they could do for the patient. These findings are consistent with previous studies that highlighted the necessity of family support by providing the family with information about the pathology of delirium and coaching families as to what the families could and should do for patients.[10,11]

The present study is preliminary and has major limitations. First, due to the moderate response rate, the responses obtained may not be representative of the entire population. Second, retrospective reporting by bereaved families could have caused recall bias. Third, some families reported that they did not recognize the patient had delirium, despite the primary treating physicians having confirmed the diagnosis. Thus, some family members might have not been able to understand and/or recognize delirium even though they were provided with both a leaflet and verbal explanation from the physicians. Fourth, the assessment instrument underwent no formal validation or reliability testing. Finally, because all patients received specialized palliative care, adherence to recommended care practice was generally high, and this may be responsible for the low sensitivity for intervention effects. Thus, the findings of the present study may not necessarily be applicable to other situations.

In conclusion, many family members of terminally ill cancer patients reported that the leaflet about delirium was very useful. This leaflet may help family members to cope with a difficult situation by facilitating accurate understanding of the situation and by helping these family members understand what they can do for the patient. More comprehensive interventions should be developed and tested in the future.

Acknowledgments

This study was supported by grants from the Ministry of Health, Labor, and Welfare of Japan. We would like to show our appreciation to Namba Miki, RN, Kaori Fukuda, RN, Meiko Kuriya, MD, Naoki Matsuo, MD, Takuya Shinjo, MD, Hiroshi Maeno, MD, Yoshikazu Chinone, MD, and Masayuki Ikenaga, MD, for carrying out this study.

Contributors: HO: conception and design, provision of the study material, collection of data, data analysis and interpretation, manuscript writing, and administrative support; TM: conception and design, provision of the study material, data analysis and interpretation, final approval of the manuscript, administrative support, and financial support; SU, RY, HH, TM, CT, and K.S: provision of the study material and final approval of the manuscript.

Author Disclosure Statement

There are no conflicts of interest.

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Original Article

Both Maintaining Hope and Preparing for Death: Effects of Physicians' and Nurses' Behaviors From Bereaved Family Members' Perspectives

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Abstract

Context. Both maintaining hope and preparing for the patient's death are important for families of terminally ill cancer patients.

Objectives. The primary aim of this study was to clarify the level of the family's achievement of maintaining hope and preparing for death and the professional's behavior related to their evaluations.

Methods. A cross-sectional, anonymous, nationwide survey was conducted involving 663 bereaved families of cancer patients who had been admitted to 100 palliative care units throughout Japan.

Results. A total of 454 family members returned the questionnaire (effective response rate, 68%). Overall, 73% of families reported that they could both maintain hope and prepare for the patient's death. The independent determinants of the family's agreement in reference to the professional's behavior are pacing the explanation with the family's preparation; coordinating patient and family discussions about priorities while the patient was in better condition; willingness to discuss alternative medicine; maximizing efforts to maintain the patient's physical strength (e.g., meals, rehabilitation); discussing specific, achievable goals; and not saying "I can no longer do anything for the patient."

Conclusion. About 20% of family members reported that they could neither "maintain hope nor prepare for death." A recommended care strategy for medical professionals could include 1) discussing achievable goals and preparing for the future and pacing explanation with the family's preparation, 2) willingness

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Accepted for publication: May 2, 2012.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2012.05.014

to discuss alternative medicine, 3) maximizing efforts to maintain the patient's physical strength, and 4) avoid saying they could do nothing further for the patient. J Pain Symptom Manage 2013;45:848–858.

Key Words
Cancer, hope, preparation, family

Introduction

Maintaining a sense of hope is important in the face of death not only for patients but also for their family members.[1–3] Although hope for a cure is often lost in the case of a terminal illness, maintaining hope is a consistently important attitude that contributes to a good death.[4,5] In an interview study with patients with incurable cancer in home care, hope was important for both a meaningful life and a dignified death.[6] Other qualitative studies indicate that hope enables patients to establish a connection with others, including medical staff, and with the future.[7,8]

However, preparing for the patient's death also is important for family members because the mental health of family members who are unprepared for the death of their loved one may suffer. In a study conducted in Canada, 90% of family members reported that it was very important to complete critical and desired tasks, resolve conflicts, and say their goodbyes toward the end of the patient's life.[9] In the U.S., 23% of bereaved families who experienced a patient death at home felt that the death of their loved one was "extremely" unexpected.[10]

Thus, these findings indicate that it is important for family members to both maintain hope and prepare for the patient's death. In the medical literature, Back[11] suggests that "hope for the best and prepare for the worst" is one of the useful strategies for approaching a patient with a life-limiting illness. The components of this strategy are to align patient and physician hopes; encourage, but not impose, the dual agenda of hoping and preparing; support the evaluation of hoping and preparing; and respect hopes and fears as well as respond to emotions. Hagerty et al.[12] reported the following actions to be hope-giving behaviors: appearing to know all about the patient's cancer, occasionally being humorous, offering to answer all the patient's questions, and saying that each day is possible and that surviving through the patient's desire to live would affect the outcome. Clayton et al.[13] reported that controlling physical symptoms, providing emotional support, preserving dignity, exploring realistic goals and discussing day-to-day living are important to maintain hope in terminally ill cancer patients and their families. Furthermore, a comprehensive literature review identified symptom control, interactions with medical health care professionals, and the health care system as contributing or threatening factors for hope.[1,3] In addition, a qualitative study suggested that to prepare family members for the patient's death, health care providers should develop a trusting relationship with the family, provide reliable information, and allow time for the family to process the information and complete important tasks.[14] Although these suggestions seem very useful, they come from anecdotal experience or small studies.[1] To date, no quantitative studies have investigated the details of how to show specific caring behavior toward family members so that they can maintain hope as well as prepare for the patient's death.

The primary aims of the present study were to 1) clarify the levels of the family's achievement of both maintaining hope and preparing for the patient's death and 2) explore the potential association between behaviors of physicians and nurses and family evaluation about achievement in maintaining hope and preparing for death. The ultimate aim of our study was to develop a care strategy for the family members of terminally ill cancer patients that makes it possible for them to both maintain hope and prepare for the patient's death.

Methods

This research was part of the Japan Hospice and Palliative Care Evaluation Study, a cross-sectional, anonymous and multicenter survey. Of 153 certified palliative care units (PCUs) of Hospice Palliative Care Japan, 95 PCUs agreed to participate in the survey.

We mailed the questionnaire to the bereaved families from participating institutions in June 2007 and again in August 2007 to the nonresponding families. A sheet explaining the aim and methods of this survey was included along with the questionnaire, and return of the questionnaire was regarded as consent to participate in the study. If the families did not want to participate in the survey, they were requested to return the questionnaire by checking the "no participation" box and the second questionnaire was not mailed. Ethical and scientific validity was confirmed by the institutional review board of each hospital.

Subjects

Primary palliative care physicians responsible for caring for the patients in PCUs identified potential participants based on the following criteria: 1) bereaved adult family members of adult cancer patients (one family member was selected for each patient), 2) capable of replying to a self-report questionnaire, 3) aware of the diagnosis of the malignancy, and 4) no serious psychological distress, as recognized by the primary palliative care physician. The last criterion, which was adopted in the same way as in our previous surveys, was applied on the assumption that primary palliative care physicians could identify families who would suffer serious psychological distress resulting from this survey because these physicians were closely involved in caring for the patient's relatives in an inpatient care setting (mean admission period, 43 days). The physicians of each participating hospital completed a list of included and excluded families and sent it to the research team after the deletion of confidential patient information.

Definition of Hope

Hope has been traditionally defined as a "multidimensional dynamic life force characterized by a confident yet uncertain expectation of achieving future good, which to the hoping person is realistically possible and personally significant."[2] For this study, hope was defined as "a process of anticipation that involves the interaction of thinking, acting, feeling, and relating and is directed toward a future fulfillment that is personally meaningful."[15]

Questionnaire

A questionnaire (available from the authors on request) was developed for this study based on a systematic literature review and discussions among the researchers.[3,6–19] Content validity was assessed by the full agreement of the authors. Face validity of the questionnaire was confirmed by a pilot test with 20 bereaved families, and all agreed the questions were easy to complete.

The primary endpoint of this study was the level of family agreement with these measures: 1) whether they could both maintain hope and prepare for the patient's death, 2) whether they could maintain hope, and 3) whether they could prepare for the patient's death. We asked the family members the following questions: "Did you both maintain hope and prepare for the patient's death?," "Did you maintain hope?," and "Did you prepare for the patient's death?" Each response was rated on a five-point scale from 1, strongly disagree, to 5, strongly agree. In the questionnaire, hope was expressed as simply "hope" (*kibo* in Japanese) without specific description of the definition.

The family members were then asked questions about 26 different behaviors of the physicians and nurses (**Table 3**) who were potential contributors to the primary endpoint. These variables were evaluated by the degree of agreement with the statement on a five-point Likert-type scale from 1, strongly disagree, to 5, strongly agree (questions 1–14), or in a yes/no format (questions 15–26). As background data, the family member reported age, gender, and relationship with the patient and interval between the patient's death and the study.

In addition, we asked the family members, "What was hope for you during the time that the patient was admitted to the palliative care unit?" They were requested to select appropriate responses from among eight choices: 1) a peaceful death, 2) (the patient) being well cared for, 3) cure or spontaneous disease remission, 4) improvement in the patient's physical condition, 5) completing certain tasks or achieving specific goals, 6) living peacefully every day, 7) emphasizing the person's worth as an individual and finding meaning in their own lives, and 8) healing relationships and spending enough time with family and friends. We chose these eight categories on the basis of a literature review and discussion among the researchers, with reference to Japanese unpublished studies.[3,6–19]

Analyses

For comparison, the respondents were classified into two groups for the primary endpoint: 1) family members who rated their agreement with maintaining a level of hope and preparing for the patient's death as "strongly agree," "agree," and "slightly agree" (agree group) and others (disagree group); 2) family members who rated their level of agreement with maintaining hope as "strongly agree," "agree," and "slightly agree" (agree group) and others (disagree group); and 3) family members who rated their level of agreement with preparing for the patient's death as "strongly agree," "agree," and "slightly agree" (agree group) and others (disagree group). These cutoff points were determined on the basis of actual data distributions, and other classifications (such as a group of strongly agree and agree vs. others) achieved essentially the same results. Using these variables as continuous variables, similar results were obtained. Univariate analyses were performed using the Mann-Whitney test, Student's t-test, or the Chi-square test, where appropriate. Multiple logistic regression analysis was then performed in a forward elimination fashion. All potential predictors identified by univariate analysis with at least marginal statistical significance ($P < 0.1$) were used in the multiple logistic regression analysis. We had decided to use the cutoff point of 0.1 to capture the variables with marginal statistical significance because of the exploratory nature of the analyses. Moreover, we similarly explored the potential associations between the components of hope and the achievement of maintaining hope and preparing for the patient's death. All analyses were performed using the Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL).

Results

Of the 663 questionnaires sent out, 487 family members responded (response rate, 73%). Thirty-three family members who responded refused to participate, and thus, we obtained 454 effective responses (effective response rate, 68%). **Table 1** summarizes the backgrounds of the patients and their bereaved families.

Level of the Family's Agreement With Their Achievement of Both Maintaining Hope and Preparing for the Patient's Death

In total, 73% of all family members ($n = 331$) reported that they could both maintain hope and prepare for the patient's death (**Table 2**). The percentage of families who could maintain hope was 58% ($n = 268$) and

Table 1

Backgrounds of Patients and Bereaved Families

Characteristics	n	%
Patients		
Age, mean ± SD (years)	70 ± 12	
Sex		
Male	251	55
Female	198	44
Primary tumor sites		
Lung	115	25
Stomach	46	10
Colon, rectum	55	12
Pancreas	39	8.6
Breast	24	5.3
Uterus, ovary	23	5.0
Others	23	5.1
Liver	20	4.4
Gallbladder, bile duct	18	4.0
Kidney, bladder	18	4.0
Esophagus	16	3.5
Prostate	16	3.5
Neck	15	3.3
Blood	5	1.0
Bone	5	1.0
Brain	9	2.0
Bereaved families		
Age, mean ± SD (years)	59 ± 13	
Sex		
Male	154	34
Female	295	65
Relationship with the patient		
Spouse	214	47
Child	153	34
Son-/daughter-in-law	31	6.8
Siblings	26	5.7
Parents	8	1.8
Others	20	4.4

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

Table 2
Primary Endpoints

	Strongly Agree	Agree	Slightly Agree	Disagree	Strongly Disagree
Outcomes			*n* (%)		
Both prepared for the patient's death and have maintained hope	59 (13)	149 (33)	123 (27)	83 (18)	19 (4.2)
Prepared for the patient's death	57 (13)	160 (35)	115 (25)	79 (17)	20 (4.4)
Maintained hope	33 (7.3)	111 (24)	124 (27)	107 (24)	32 (7.0)

the percentage of families who could prepare for the patient's death was 73% ($n = 332$).

Family-Reported Behaviors of Physicians and Nurses

Table 3 shows the percentage of family members who agreed with each statement. More than 80% of respondents reported that physicians and nurses respected the individual ideas of the patients and family members that might improve the patient's physical condition, were knowledgeable about the most advanced treatments available, adapted the treatment goals and methods to the circumstances, and discussed both specific and achievable goals with the patient and the family members.

Less than 10% of respondents reported negative behaviors on the part of physicians and nurses, such as saying "I can no longer do anything for the patient," suddenly telling family members to prepare for the patient's death just before death rather than introducing the issue at an earlier time, providing all information although the patient or family members did not request it, and giving only good news and no bad news.

Family Members and the Components of Their "Hope"

In total, 59% of family member respondents ($n = 267$) reported that they had hoped for a peaceful death, 50% ($n = 227$) hoped for the patient to be well cared for, 47% ($n = 215$) hoped for healing of relationships and spending enough time with family and friends, 35% ($n = 160$) hoped for living

Table 3
Behavior of Physicians and Nurses

Items	*n* (%)
Respected the individual ideas given by the patients and family members to improve physical condition	387 (86)
Knowledgeable about the most advanced treatment	383 (85)
Flexibly adopted the treatment goals and methods to the circumstances	380 (84)
Discussed with the patient and family members specific and achievable goals	371 (81)
Discussed with the patient and family members about completing the desired tasks	357 (78)
Paced the explanation with the state of the family's preparation	352 (78)
Allowed to satisfactorily receive anticancer treatments	335 (74)
Made maximum efforts to maintain patient's physical strength, such as through meals and rehabilitation	317 (70)
Presented several options of medical treatment to choose from for the patient and family	302 (67)
Coordinated care plans for the patient to stay at home	287 (63)
Coordinated discussion with the patient and family about their priorities while the patient was in better condition	261 (58)
Willingly spoke about alternative medicine	241 (53)
Informed patient and family of defined predicted survival without ranges	202 (45)
Told that the estimated prognosis was based on average outcomes and would not necessarily apply to the patient	189 (42)
Provided predicted outcomes about daily life, not of survival time itself	163 (36)
Told "anticancer treatment might be possible if the patient's condition improves" or "new anticancer treatment would be available in the future"	79 (17)
Told that "the patient's condition will definitely not improve"	76 (17)
Told that medical treatments the patient had received were problematic	58 (13)
Told that some patients live long even without antitancer treatment	57 (13)
Explained the same points many times so as to convince the family	57 (13)
Indicated that they assumed the patient was going to die	54 (12)
Told the patient and family that their expectation was absolutely impossible to achieve	54 (12)
Said "I can no longer do anything for the patient"	43 (9)
Suddenly recommended that the family members prepare for the patient's death	27 (6)
Provided information that the patient or family members did not request	27 (6)
Gave only good news and no bad news	19 (4)

Percentage indicates the response with "strongly agree," "agree," "slightly agree" on a five-point Likert-type scale and a "yes" for yes/no format questions.

peacefully every day, 19% ($n = 88$) emphasized the person's worth as an individual and finding meaning in their own life, 13% ($n = 57$) hoped for an improvement in the patient's physical condition, 9.5% ($n = 43$) hoped for completing certain events or achieving specific goals, and 1.3% ($n = 6$) hoped for cure or spontaneous disease remission.

In multivariate models, families who hoped for a peaceful death, the patient to be well cared for, and healing of relationships and spending enough time with family and friends were significantly highly likely to achieve maintaining hope and preparing for the patient's death (**Table 4**). The number of hope components was significantly larger in the family members who reported they could both maintain hope and prepare for the patient's death than those who did not (2.8 ± 1.9 vs. 0.83 ± 1.6; $P < 0.001$).

Determinants of the Family's Level of Achievement of Maintaining Hope and Preparing for the Patient's Death Through the Behavior of Professionals

Univariate analysis revealed the determinants of the family's level of achievement of maintaining hope and preparing for the patient's death (**Table 5**). Multiple logistic regression analysis showed that independent determinants of a family's agreement about achieving a good level of maintaining hope and preparing for the patient's death were pacing the explanation in accord with the state of the family's preparation, coordinating a patient-family discussion about their priorities while the patient was still in better condition, willingness to talk about the concerns of both patients and family members about alternative medicine, maximizing efforts to maintain the patient's physical strength including making arrangements for meals and rehabilitation sessions, holding discussions with the patient and family members about both specific and achievable goals, and not saying that they could no longer do anything for the patient (**Table 6**).

Discussion

To our knowledge, this was the first quantitative study to investigate family members' achievement of both maintaining hope and preparing for the patient's death. The first important finding was that about 20% of family members reported that they could neither "maintain hope nor prepare for the patient's death." This is consistent with previous studies that suggested a considerable number of family members felt hopelessness or unpreparedness.[10,16,17] These findings suggest that about 20% of families of terminally ill cancer patients experienced either hopelessness or unpreparedness, even if they received specialized palliative or hospice care. Thus, more effort may be needed to improve the professional practices that support the achievement of the family both maintaining hope and preparing for the death.

The second and the most important finding of this study was the identification of behavioral factors by medical professionals related to family members' achievement of maintaining hope and preparing for the death. The relevant factors include 1) pacing the explanation in accordance with the state of the family's preparation, 2) coordinating discussions so that the patient and the family members could discuss their priorities while the patient was in better condition, 3) willingness to talk about alternative medicine, 4) maximizing efforts to maintain the patient's physical strength, 5) not saying "I can no longer do anything for the patient," and 6) discussing specific and achievable goals.

Discussing Achievable Goals and Preparing for the Future and Pacing the Explanation in Accordance With the State of the Family's Preparation

In this study, 78% of family members reported that health care providers paced the explanation according to the state of the family's preparation. This perception was significantly associated with the family's achievement of both maintaining hope and preparing for the patient's death. This finding is consistent with previous studies,[18] and these results confirm that providing information with careful consideration of the family's preparation is an important strategy in communicating bad news.

About 58% of family members in this study reported that health care providers coordinated the patient and family discussion about priorities while the patient was in better

Table 4
Associations Between Components of Hope and Achievement of Both Maintaining Hope and Preparing for the Patient's Death

	Univariate Analyses		Multivariate Analyses					
			Model 1 ($R^2 = 0.33$)		Model 2 ($R^2 = 0.32$)		Model 3 ($R^2 = 0.28$)	
Components of Hope	Achieved, *n* (%)	*P*	Odds Ratio (95% CIs)	*P*	Odds Ratio (95% CIs)	*P*	Odds Ratio (95% CIs)	*P*
Peaceful death		<0.001	6.8 (3.6–13)	<0.001	7.4 (3.7–15)	<0.001	Not included	
Presence (*n* = 257)	239 (93)							
Absence (*n* = 176)	92 (53)							
Well cared for		<0.001			2.3 (1.1–4.7)	0.020	3.8 (2.0–7.1)	<0.001
Presence (*n* = 218)	201 (92)							
Absence (*n* = 215)	130 (60)							
Spending enough time with family and friends		<0.001	3.1 (1.5–6.3)	0.001	Not included		4.7 (2.4–9.1)	<0.001
Presence (*n* = 208)	197 (95)							
Absence (*n* = 225)	137 (61)							
Living peacefully everyday		<0.001						
Presence (*n* = 155)	140 (90)							
Absence (*n* = 278)	191 (69)							
Worth as an individual and meaning		<0.001						
Presence (*n* = 86)	81 (94)							
Absence (*n* = 347)	250 (72)							
Improvement in physical condition		0.11						
Presence (*n* = 54)	46 (85)							
Absence (*n* = 379)	285 (75)							
Achieving specific goals		0.24						
Presence (*n* = 43)	36 (84)							
Absence (*n* = 390)	295 (76)							
Cure		1.0						
Presence (*n* = 5)	4 (80)							
Absence (*n* = 428)	327 (76)							

CI = confidence interval.
The sums of data do not add up to 100% because of missing values.

Table 5
Univariate Analysis

	Both Prepared for the Patient's Death and Maintained Hope			Prepared for the Patient's Death			Maintained Hope		
Factors	Agree ($n = 331$)	Disagree ($n = 102$)	P	Agree ($n = 332$)	Disagree ($n = 99$)	P	Agree ($n = 268$)	Disagree ($n = 139$)	P
Knowledgeable about the most advanced treatment, *n* (%)	294 (89)	73 (71)	<0.01	294 (89)	74 (75)	<0.01	239 (89)	107 (77)	<0.01
Allowed patients to satisfactorily receive anticancer treatment, *n* (%)	264 (80)	59 (58)	<0.01	257 (77)	63 (64)	<0.01	216 (81)	88 (63)	<0.01
Told that the medical treatments the patient had received were problematic, *n* (%)	39 (12)	19 (19)	0.09	37 (11)	18 (18)	0.09	30 (11)	24 (17)	0.09
Presented several options to choose from for the patient and family, *n* (%)	230 (70)	62 (62)	0.03	234 (70)	57 (58)	<0.01	199 (74)	81 (58)	<0.01
Respected the ideas of the patients and family members to improve the patient's physical condition, *n* (%)	295 (89)	80 (78)	<0.01	292 (88)	80 (80)	<0.01	240 (90)	115 (83)	0.03
Willingly spoke about alternative medicine, *n* (%)	200 (60)	36 (35)	<0.01	194 (58)	40 (40)	<0.01	164 (61)	63 (45)	<0.01
Made maximum efforts to maintain patient's physical strength (e.g., meals, rehabilitation), *n* (%)	248 (75)	57 (56)	<0.01	245 (74)	59 (60)	<0.01	212 (79)	78 (56)	<0.01
Discussed with the patient and family members about completing all the desired tasks, *n* (%)	276 (83)	69 (68)	<0.01	279 (84)	66 (67)	<0.01	237 (88)	96 (69)	<0.01
Flexibly adopted the treatment goals and methods to the circumstances, *n* (%)	289 (87)	76 (75)	<0.01	290 (87)	73 (74)	<0.01	241 (90)	108 (78)	<0.01
Coordinated care plans for the patient to stay at home as long as possible, *n* (%)	223 (67)	57 (56)	<0.01	224 (67)	56 (57)	0.01	187 (70)	82 (59)	<0.01
Discussed specific and achievable goals with the patient and family members, *n* (%)	282 (85)	75 (74)	<0.01	284 (86)	73 (74)	<0.01	239 (89)	103 (74)	<0.01
Told the patient and family that their expectations were absolutely impossible to achieve, *n* (%)	35 (11)	16 (16)	0.16	35 (11)	15 (15)	0.21	23 (8.6)	25 (18)	<0.01
Said, "I can no longer do anything for the patient," *n* (%)	25 (7.5)	18 (18)	<0.01	22 (6.6)	19 (19)	0.01	13 (4.9)	27 (19)	<0.01
Indicated that they assumed the patient was going to die, *n* (%)	32 (9.7)	20 (20)	<0.01	28 (8.4)	23 (23)	<0.01	21 (7.8)	27 (19)	<0.01
Paced the explanation with the state of the family's preparation, *n* (%)	275 (83)	65 (63)	<0.01	281 (85)	57 (58)	<0.01	229 (85)	91 (65)	<0.01
Explained the same points many times so as to convince the family, *n* (%)	42 (12)	14 (14)	0.74	46 (14)	10 (10)	0.37	37 (14)	14 (10)	0.28
Provided all information although the patient or family members did not request it, *n* (%)	15 (5.5)	11 (11)	0.02	20 (6)	7 (7)	0.66	11 (41)	14 (10)	0.02
Gave only good news and no bad news, *n* (%)	15 (4.5)	3 (2.9)	0.48	13 (39)	4 (4)	0.95	11 (4.1)	5 (3.6)	0.81
Said that "the estimated prognosis was based on average outcomes and would not necessarily apply to the patient," *n* (%)	138 (42)	45 (44)	0.71	143 (43)	41 (41)	0.68	130 (49)	50 (36)	0.01
Said that "anticancer treatment might be possible if the patient's condition improves," *n* (%)	67 (20)	12 (12)	0.04	61 (18)	16 (16)	0.53	56 (21)	18 (13)	0.04

(*Continued*)

Table 5
Continued

	Both Prepared for the Patient's Death and Maintained Hope			Prepared for the Patient's Death			Maintained Hope		
Factors	Agree ($n = 331$)	Disagree ($n = 102$)	P	Agree ($n = 332$)	Disagree ($n = 99$)	P	Agree ($n = 268$)	Disagree ($n = 139$)	P
Said that "some patients live long even without anticancer treatment," n (%)	47 (14)	9 (8.8)	0.13	42 (13)	12 (12)	0.8	40 (15)	16 (12)	0.35
Informed patient and family of definite predicted survival without ranges and uncertainties, n (%)	150 (45)	46 (45)	0.9	148 (45)	49 (49)	0.47	122 (46)	69 (50)	0.43
Explained predicted outcomes in terms of daily life, not survival time itself, n (%)	129 (39)	29 (28)	0.05	130 (39)	29 (29)	0.09	119 (44)	34 (24)	<0.01
Clearly stated that "the patient's condition definitely does not seem to improve," n (%)	53 (16)	22 (22)	0.13	51 (15)	25 (25)	0.02	42 (16)	32 (23)	0.05
Coordinated the discussion of the patient and family about their priorities while the patient was in better condition, n (%)	219 (66)	36 (35)	<0.01	220 (66)	35 (35)	<0.01	184 (69)	56 (40)	<0.01
Suddenly recommended that the family prepare for the patient's death just before the patient's death, n (%)	19 (5.7)	8 (7.8)	0.41	19 (6)	8 (8)	0.32	13 (4.9)	12 (8.6)	0.11

condition. A previous study revealed that 90% of the family members of seriously ill patients reported that one of the most important elements related to quality end-of-life care is to complete things.[9,19] Also, a previous study suggested that to explore achievable short-term goals is important in end-of-life communication.[13] These results support the idea of a redefined future in terms such as days and achievable short-term goals as a way to improve the sense of hope; this can be helpful for both the patient and family members to feel supported in end-of-life care.[2]

Willingness to Discuss Alternative Medicine

In the present study, about 58% of family members reported that health care providers willingly spoke about alternative medicine. Alternative medicine is widely used according to a European survey; about 35% of cancer patients use some form of alternative medicine. Most patients use alternative medicine to improve physical and emotional well-being,[20] but many do not disclose their use of alternative medicine to their oncologists.[21] A nationwide survey in Japan showed that about 80% of oncologists believed that alternative medicine is ineffective against cancer.[22] The present study suggests that communication about alternative medicine in and of itself, not always focusing on the treatment effect, might contribute to facilitating a sense of hope for some family members. That is, communicating about alternative medicine may lead to exploring the family's real concerns and help families find methods other than alternative medicine for maintaining hope.

Maximizing Efforts to Maintain the Patient's Physical Strength

A relative being unable to take nourishment orally is perceived by most family members as a cause of emotional distress. In a study in Japan, about 70% of family members experienced a high level of emotional distress about the patient's lowered oral intake and felt a sense of helplessness and guilt.[23] The role of rehabilitation in the care of terminally ill patients is to improve the patient's level of physical function and comfort, which should be maintained as long as possible to improve their quality of life and reduce the burden of their caregivers.[24] This study confirms that discussion with family members

Table 6
Multivariate Analysis

	Both Prepared for the Patient's Death and Maintained Hope[a]			Prepared for the Patient's Death[b]			Maintained Hope[c]		
Factors	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Paced the explanation with the state of the family's preparation				2.6	1.3–5.3	<0.01			
Coordinated the discussion of the patient and family about their priorities while the patient was in a better condition	3.9	2.1–7.0	<0.01	2.6	1.4–4.8	<0.01	2.3	1.3–4.1	<0.01
Willingness to talk about the concerns of the patient and family members as well as about alternative medicine	3.1	1.8–5.4	<0.01	2.2	1.3–3.6	<0.01			
Made maximum efforts to maintain the patient's physical strength, such as meals and rehabilitation							1.9	2.3–3.0	0.012
Discussed specific and achievable goals with the patient and family members							1.9	1.1–3.3	0.016
Said, "I can no longer do anything for the patient"				0.5	0.27–0.94	0.03	0.32	0.15–0.68	<0.01

Values are expressed as adjusted odds ratios with CIs for only statistically significant items.
[a]$R^2 = 0.26$.
[b]$R^2 = 0.24$.
[c]$R^2 = 0.25$.

about maintaining the patient's physical strength, especially in collaboration with other medical staff members, such as dieticians and physical therapists, is important for maintaining hope.

Not Saying "I Can No Longer Do Anything for the Patient"

Published guidelines strongly recommend that physicians should not say that they have nothing more to provide for patients and that physicians should ensure there is always something to be done, such as symptom palliation and emotional support.[11,25] The present study reconfirmed that to maintain hope and prepare for the patient's death, health care providers should ensure that they continue to do their best for the patient through refocusing goals, instead of saying that they can do nothing more for the patient.

In addition, the finding that components of hope, such as hope for a peaceful death, that the patient be well cared for, and spending enough time with family, were significantly associated with higher achievement of maintaining hope and preparing for the patient's death suggests that clinicians could support the family by emphasizing symptom alleviation, assuring that the patient is well cared for, and confirming time for patients and families.

This study had several limitations. First, because this study focused on family members' experiences, the concordance between families' and patients' evaluations was unexplored, and thus, the findings from this study do not necessarily correspond to the patients' evaluations. Second, the subjects of this study were limited to the family members of patients who received specialized palliative care; therefore, these findings might not be applicable to family members in other settings. Third, there may have been recall bias because of the retrospective design of the study. Fourth, to measure the levels of the family's achievement of maintaining hope and preparing for death, we used three questions, each from validated instruments. These three items might have overlapped in concept, and the overlap may have influenced the results. Fifth, there may be potential selection bias as a result of the physician-selected population.

In conclusion, about 20% of family members reported that they could neither maintain hope nor prepare for the patient's death. On the basis of this study, we propose a care strategy that medical professionals adopt for family members of terminally ill cancer patients so that they will both maintain hope and prepare for the patient's death; this strategy includes the following behavior of the part of professionals: 1) discuss achievable goals and preparations for the future and pace explanations with the family's preparation, 2) be willing to talk about alternative medicine, 3) expend maximum effort to maintain the patient's physical strength, and 4) avoid saying that nothing more can be done for the patient. Further research should focus on a patient survey, a non-Asian population, and effects of the intervention developed from this study finding.

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Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(9)896–909
doi:10.1093/jjco/hyt099
Advance Access Publication 23 July 2013

Clinical Guideline for Pharmacological Management of Cancer Pain: The Japanese Society of Palliative Medicine Recommendations

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Received October 3, 2012; accepted June 18, 2013

Pain is the most frequent and distressing symptom in cancer patients. As part of a worldwide effort to improve the quality of pain control, several clinical guidelines for the management of cancer pain have been published and revised in the last decade. The Japanese Society of Palliative Medicine first published a Japanese clinical guideline for the management of cancer pain in 2000. Since then, many clinical studies concerning cancer pain management have been conducted, new drugs have become available in Japan and the methodology of developing a guideline has been refined. Therefore, we decided to develop a novel clinical guideline. This review paper summarizes the recommendations and the rationales of this new clinical guideline for the pharmacological management of cancer pain. In addition, a short summary of the clinical guideline development process is provided. This new Japanese Society of Palliative Medicine guideline highlights the importance of conducting well-designed studies to identify the best practices in cancer pain management.

Key words: cancer pain – opioid analgesics – nonopioid analgesics – guideline

INTRODUCTION

Pain is the most distressing symptom in cancer patients, and it affects 70–80% of patients with advanced disease (1). Current evidence from countries including Japan suggests that many cancer patients suffer from pain and do not receive adequate pain relief (2–7). As part of a worldwide effort to improve the quality of pain control, several clinical guidelines for the management of cancer pain have been published and revised in the last decade (8–13). As one of such efforts, the Japanese Society of Palliative Medicine (JSPM) first published a Japanese clinical guideline for the management of cancer pain in 2000 (14). Although a formal systematic review was conducted, recommendations of the JSPM guideline in 2000 were the same as the existing guidelines and the grading system of recommendations was anecdotal. Since then, many clinical studies concerning cancer pain management have been conducted, and new drugs have become available in Japan. In addition, the methodology of developing a guideline has been refined (15,16). A novel clinical guideline to integrate new findings using the validated methodology is warranted.

This review paper summarizes the recommendations and the rationales for this new clinical guideline for the pharmacological management of cancer pain. In addition, a short summary of the development process for this guideline is provided.

SHORT SUMMARY OF THE DEVELOPMENT PROCESS

The objective of developing the guideline was to establish the standard pharmacological management of cancer pain. The target population includes all cancer patients who experience pain, whereas the primary users of this guideline are all medical personnel who care for cancer patients, including palliative care physicians, oncologists, nurses and pharmacists.

TASK FORCE

The committee of JSPM nominated the task force members from a pool of specialists with adequate clinical experience to cover multidisciplinary areas, and the JSPM Board gave the final approval. The task force comprised 56 physicians (31 palliative care physicians, 15 anesthesiologists, 5 oncologists and 5 home care physicians), 25 pharmacists, 23 nurses, 1 epidemiologist and 7 other professionals (Appendix).

SYSTEMATIC LITERATURE REVIEW

First, the task force gathered clinical questions by administering a questionnaire to all members of the task force. These items were then restructured into 65 questions. Next, the task force performed a systematic literature review of each clinical question using the electronic search function in the PubMed database; a manual search of all articles published in the *Journal of Pain and Symptom Management* and *Palliative Medicine* from January 2000 to July 2008, a search of the PaPaS (Pain, Palliative and Supportive Care) category of the Cochrane database and a review of reference literature of relevant guidelines (8–13) and textbooks (17–22). This review process included only studies that evaluated drugs available in Japan. The abstracts of all identified literature references were read, and the full text of all relevant literature was reviewed.

DRAFTING RECOMMENDATIONS AND DELPHI METHODS

Each member in charge of a clinical question drafted the recommendations and general background descriptions. The Delphi method was then performed to examine the validity of each statement. The Delphi method is a standardized method used to reach consensus; we used the modified Delphi method (23). All statements in the clinical guideline were separated into >150 meaningful units, and the task force members were requested to rate the validity of all statements on a nine-point Likert-type scale from one (inappropriate) to nine (appropriate). After three Delphi rounds and an external review by 12 external reviewers (5 palliative care physicians, 2 radiation oncologists, 1 anesthesiologist, 1 home care physician, 1 nurse, 1 pharmacist and 1 epidemiologist), the final version was established.

EVIDENCE AND RECOMMENDATION LEVELS

The task force decided to use an original recommendation table for this clinical guideline, following the concepts from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to articulate the levels of evidence and the strengths of each recommendation (Table 1) (15). We decided to use 'should' for expressing recommendation strength 1 and 'may' for recommendation strength 2 in this paper.

RECOMMENDATIONS

We created 65 recommendations: 24 for the general management of cancer pain, 24 for the management of pain from specific etiologies, 15 for the management of opioid-induced adverse effects and 2 for patient education. This guideline also included chapters on general background descriptions, flow charts to visualize the recommendations, a complete reference list followed by the search strategy and a summary of other related international guidelines that have previously been published.

Table 2 demonstrates all the recommendations listed in the guideline, and Fig. 1 shows an overview and the main algorithm for using those recommendations.

The key recommendations and their rationales are described below.

Table 1. Recommendation table

Strength of recommendation	
1 (strong)	Recommended treatment is certainly of benefit to the patient, and the benefit exceeds the harm or burden. In the statement, 'should' is used.
2 (week)	Recommended treatment may be of benefit to the patient. Or the benefit competes with the harm or burden from the recommended treatment. In the statement, 'may' is used.
Level of evidence	
A (high)	The evidence from the results of studies is established. The result will not change, even if further study is performed, e.g. multiple high-quality randomized controlled trials with concordant results, or a meta-analysis of randomized controlled trials
B (low)	Although some studies support the result, evidence is not enough. Further study may change the result, e.g. randomized, controlled trials with inconsistent results, low-quality randomized controlled trials, small number of randomized controlled trials, non-randomized controlled trials or multiple observational trials with consistent results
C (very low)	There is insufficient evidence for the result, e.g. small number of observational trials, case reports and expert opinions

Table 2. Recommendations in the guideline of the Japanese Society of Palliative Medicine

1. Management of cancer pain
  1.1 Assessment
    1.1.1 Comprehensive assessment of pain should be carried out.
  1.2 Patients with mild pain
    1.2.1 Acetaminophen should be administered to cancer patients with mild pain [1A].
    1.2.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be administered to cancer patients with mild pain [1B].
    1.2.3 The type of non-opioid analgesic should be chosen in accordance with the effectiveness and tolerability of an individual patient [1A].
    1.2.4 Prostaglandin E1 analogs, proton pump inhibitors or H2 receptor blockers should be used for the prevention of peptic ulcer in patients who are treated with an NSAID [1A].
  1.3 Patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics
    1.3.1 Opioids should be administered to cancer patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics [1B].
    1.3.2 The type of opioid should be chosen individually according to the patient's condition [1B].
    1.3.3 In cancer patients with stable and mild-to-moderate pain, either sustained-release or immediate-release opioids may be used. In cancer patients with severe or unstable pain, immediate-release opioids or parenteral opioids may be used [2B].
    1.3.4 Patients should be carefully assessed and observed for nausea/vomiting during opioid therapy, and antiemetics should be readily available whenever nausea/vomiting occurs [1C].
    1.3.5 Patients should be carefully assessed and observed for constipation during opioid therapy; moreover, they should be provided with instructions regarding adequate fluid intake, diet and laxatives for the prevention of constipation [1C].
    1.3.6 Nonopioid analgesics may be continued when opioids are introduced in patients with inadequate pain control by nonopioid analgesics [2B].
  1.4 Patients with inadequately controlled pain despite initial opioid use
    1.4.1 Non-opioid analgesics should be used concurrently with opioids in patients who experience continuous pain with regular opioid use [1A].
    1.4.2 The dose of regular opioid should be increased in patients who experience continuous pain with regular opioid use [1B].
    1.4.3 Type of opioid should be switched in patients with inadequately controlled pain under a certain type of opioids [1B].
    1.4.4 Another type of opioid may be added in patients with inadequate pain control by a certain type of opioid [2C].
    1.4.5 The administration route may be changed to intravenous or subcutaneous infusion in patients with inadequate pain control with an oral or a transdermal preparation of opioid analgesics [2C].
    1.4.6 Ketamine may be used in combination with opioids in patients with inadequately controlled pain after a sufficient increase in opioid dose [2B].
    1.4.7 Corticosteroids may be used in combination with opioids only for particular pain etiologies, paying careful attention to the risk of adverse reactions in patients who experience pain after a sufficient increase in opioid dose [2C].
  1.5 Patients with breakthrough pain
    1.5.1 The rescue dose of opioids should be used in patients with breakthrough pain [1B].
    1.5.2 The rescue dose may be increased if adverse events are acceptable and the initial rescue dose provides inadequate analgesic effects [2C].
    1.5.3 For patients with end-of-dose failure, the dose of regular opioids should be increased or interval of regular opioids should be shortened [1B].
2. Treatment of pain from specific etiology
  2.1 Neuropathic cancer pain
    2.1.1 Any of the adjuvant analgesics (anticonvulsants, antidepressants, antiarrhythmics, ketamines or corticosteroids) may be used in cancer patients with neuropathic pain [2B].
    2.1.2 Another type of adjuvant analgesics may be added in patients with inadequate control of neuropathic pain after increasing the dose of a certain adjuvant analgesic sufficiently, in consultation with an expert [2C].
  2.2 Bone metastatic pain
    2.2.1 Bisphosphonate may be used in patients with pain from bone metastasis, in consideration of expected prognosis [2B].
  2.3 Epigastric pain due to pancreatic cancer
    2.3.1 Celiac plexus block may be performed in patients with epigastric pain due to pancreas cancer [2A].
  2.4 Pain in the thoracic area
    2.4.1 Nerve block (such as epidural block, intercostals nerve block, nerve root block or intrathecal phenol block) may be performed in patients with pain in the thoracic area [2C].

Continued

Table 2. *Continued*

2.5 Perineal pain

2.5.1 Saddle block or superior hypogastric plexus block may be performed in patients with perineal pain [2C].

2.6 Pain from malignant psoas syndrome

2.6.1 Muscle relaxants may be used in patients with malignant psoas syndrome [2C].

2.6.2 Nerve block (such as epidural block or nerve root block) may be performed in patients with malignant psoas syndrome [2C].

2.7 Pain from malignant bowel obstruction

2.7.1 Octreotide or scopolamine butylbromide may be used in patients with pain from malignant bowel obstruction [2B].

2.7.2 Corticosteroids may be used in patients with pain from malignant bowel obstruction [2B].

3. Treatment of adverse events of opioids

3.1 Nausea/vomiting

3.1.1 Etiology of nausea/vomiting should be assessed, and any reversible etiology should be treated.

3.1.2 Anti-emetics should be used in patients developing nausea/vomiting on opioids. Type of anti-emetics should be chosen from anti-dopaminegics, prokinetics, or antihistaminics [1C].

3.1.3 Type of opioids should be switched to another in patients developing nausea/vomiting on a certain opioid [1B].

3.1.4 Administration route may be changed to intravenous or subcutaneous infusion in patients developing nausea/vomiting on oral opioids [2C].

3.2 Constipation

3.2.1 Etiology of constipation should be assessed, and any reversible etiology, especially fecal impaction or bowel obstruction, should be treated.

3.2.2 Laxatives should be used in patients developing constipation on opioids [1B].

3.2.3 Type of opioids should be switched to fentanyl in patients on morphine or oxycodone with refractory constipation after laxatives [1B].

3.3 Drowsiness

3.3.1 Etiology of drowsiness should be assessed, and any reversible etiology should be treated. The possibility of opioid overdose should also be assessed.

3.3.2 Psycho-stimulants may be used in patients developing drowsiness on opioids, in consultation with an expert [2C].

3.3.3 Type of opioids should be switched to another in patients with drowsiness on a certain opioid [1B].

3.3.4 Administration route may be changed to intravenous or subcutaneous infusion in patients developing drowsiness on oral opioids [2C].

3.4 Delirium

3.4.1 Etiology of delirium should be assessed, and any reversible etiology should be treated.

3.4.2 Anti-psychotics may be used in patients developing delirium on opioids [2B].

3.4.3 Type of opioids should be switched to another in patients with delirium on a certain opioid [1B].

3.4.4 Administration route may be changed to intravenous or subcutaneous infusion in patients developing delirium on oral opioids [2C].

4. Patient education in cancer pain management

4.1.1 Patients should be given education about cancer pain management [1A].

JSPM, Japanese Society of Palliative Medicine

ASSESSMENT OF CANCER PAIN

(i) A comprehensive assessment of the pain should be performed. A comprehensive assessment includes an assessment of the etiology of the pain and that of the pain itself.

The influence of the pain on daily life; the pattern, intensity, location and quality of pain; and the exacerbating/relieving factors should be evaluated. In addition, the response to current treatment and the effectiveness of a rescue dose should be evaluated.

For assessing the etiology of cancer-related pain, it is important to evaluate whether it is directly related to the cancer itself and/or to its treatment. In addition, it is important to evaluate whether the pain is a sign of an oncological emergency and identify its etiology (e.g. neuropathic pain, bone pain and perineal pain). This assessment includes history, physical examinations and imaging studies, and it must lead to a therapeutic approach.

PATIENTS WITH MILD PAIN

(i) Acetaminophen should be administered to cancer patients with mild pain. [1A]

A randomized controlled trial of patients with advanced cancer demonstrated that acetaminophen decreased pain intensity to a significantly greater extent than placebo (24). A Cochrane review also concluded that acetaminophen is more effective than placebo in improving cancer pain (25).

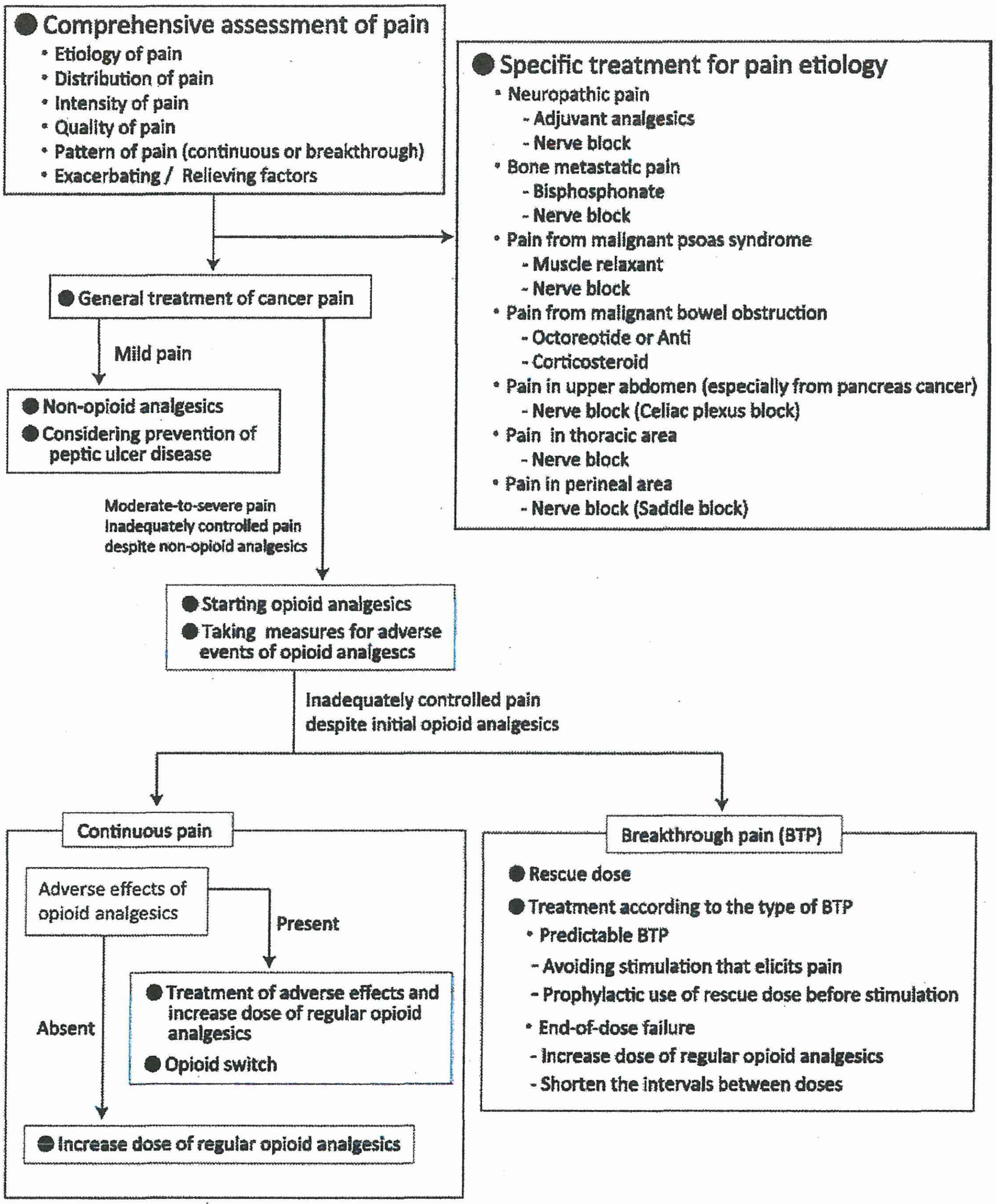

Figure 1. Overview of recommendations.

Because the available evidence shows that acetaminophen decreases pain in cancer patients who are not prescribed any analgesics, the panel has agreed that acetaminophen should be administered to cancer patients with mild pain.

(ii) Non-steroidal anti-inflammatory drugs should be administered to cancer patients with mild pain. [1B]

Several small, randomized controlled trials demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) decreased pain intensity in cancer patients to a significantly greater extent than placebo (26–28). A recent systematic review, including seven randomized controlled trials, concluded that NSAIDs are more effective than placebo in improving cancer pain (25).

Because the available evidence demonstrates that NSAIDs decrease pain in cancer patients who are not prescribed any analgesics, the panel has agreed that NSAIDs should be administered to cancer patients with mild pain.

(iii) The nonopioid analgesic type should be chosen in accordance with the effectiveness and tolerability of an individual patient. [1A]

Several small studies comparing different nonopioid analgesics demonstrated no significant difference in the effectiveness in treating cancer pain and the incidence of adverse events (29–32). A systematic review concluded that there is no evidence of the superiority of certain nonopioid analgesics over others (25).

Because the available evidence shows no superiority of certain nonopioid analgesics over others in terms of either efficacy or adverse event profile, the panel has agreed that the type of nonopioid analgesic should be chosen in accordance with the effectiveness and tolerability of an individual patient (e.g. renal function, risk of peptic ulcer, and bleeding tendency).

(iv) Prostaglandin E1 analogs, proton pump inhibitors, or H2 receptor blockers should be used for the prevention of peptic ulcer in patients who are treated with an NSAID. [1A]

According to the Evidence-Based Guideline for Gastric Ulcer in Japan (33), the efficacy of prostaglandin E1 analogs, proton pump inhibitors and high-dose H2 receptor blockers for the prophylaxis of NSAID-induced peptic ulcer has been demonstrated in several randomized controlled trials and systematic reviews.

Therefore, prostaglandin E1 analogs, proton pump inhibitors, or H2 receptor blockers should be used for the prevention of peptic ulcer in patients who are treated with an NSAID.

Patients with Moderate-to-severe Pain or Inadequately Controlled Pain Despite Treatment with Nonopioid Analgesics

(i) Opioids should be administered to cancer patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics. [1B]

For patients with moderate-to-severe pain or inadequate pain control with a nonopioid analgesic, the World Health Organization (WHO) guideline recommends the use of Step 2 opioids first, and switching to Step 3 opioids (3-step strategy) afterward. Several observational studies have revealed the efficacy of this WHO analgesic ladder (34,35). Therefore, using the three-step strategy is likely to be safe and effective.

On the other hand, two randomized controlled trials demonstrated that using a Step 3 opioid first (two-step strategy) is significantly more effective than using the three-step strategy, in improving cancer pain (36,37). However, some adverse events such as nausea or constipation tended to be more frequent in the two-step strategy group in these studies.

Available evidence suggests that the three-step strategy is effective without troublesome adverse events, and the two-step strategy is more effective than the three-step strategy, but with more adverse events. Therefore, opioids should be administered to cancer patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics, using both the three-step and two-step strategies.

(ii) The type of opioid should be chosen individually according to the patient's condition (i.e. availability of administration route, medical complications, coexisting symptoms and pain intensity). [1B]

A Cochrane review including 54 randomized controlled trials concluded that morphine is effective in improving cancer pain (38).

The efficacy of using oxycodone was evaluated in an observational trial including 390 cancer patients with moderate-to-severe pain (39). In this trial, the intensity of pain was significantly decreased after the administration of oxycodone, and there were no serious adverse events. A systematic review of four studies comparing oxycodone and morphine concluded that oxycodone is as effective as morphine in improving cancer pain (40). Also, a recent, small, randomized, controlled trial comparing the effectiveness of sustained-release oxycodone with that of sustained-release morphine in improving cancer pain demonstrated that these two preparations exerted an approximately equivalent analgesic effect (41).

Four randomized controlled trials comparing the efficacy of morphine with that of transdermal or intravenous fentanyl demonstrated no significant difference in analgesic effect between the groups (42–45). Two of these four studies demonstrated that the incidence of constipation was significantly lower in the fentanyl group than in the morphine group. Among the empirical studies using transdermal fentanyl as the initial opioid, two observational studies demonstrated that the intensity of pain decreased in a majority of patients, without the presence of serious adverse events (46,47). A randomized controlled trial comparing the efficacy of transdermal fentanyl with that of sustained-release morphine as the initial opioid in patients with mild-to-moderate pain demonstrated no significant difference in analgesic effect between the groups in the transdermal fentanyl group (48).

Available evidence showed no significant differences between morphine, oxycodone and fentanyl, regarding the efficacy. Therefore, the type of opioids should be chosen individually according to the patient's condition.

The administration route chosen should be the one most convenient and preferable to the patient. In general, the oral route is preferred. In case of difficulty in using the oral route, continuous parenteral infusion or transdermal or rectal routes can be chosen according to patient's preference.

Regarding complications, morphine is best avoided in patients with renal insufficiency because accumulation of active metabolites can lead to adverse events (49). Regarding coexisting symptoms, fentanyl causes constipation less frequently than other opioids (44,45,48); therefore, fentanyl is preferable in patients with severe constipation or those who need to avoid a decrease in bowel movements. Morphine has been demonstrated to be effective in alleviating dyspnea in cancer patients (50); therefore, morphine is preferable in patients with dyspnea.

Regarding pain intensity, adjusting the dose of transdermal fentanyl within short time intervals is difficult because of its long half-life. Therefore, transdermal fentanyl should not be used as the initial opioid in patients with severe or unstable pain.

(iii) In cancer patients with stable and mild-to-moderate pain, either sustained-release or immediate-release opioids may be used. In cancer patients with severe or unstable pain, immediate-release opioids or parenteral opioids may be used. [2B]

A Cochrane review analyzed 15 randomized controlled trials that compared the efficacy of immediate-release and sustained-release morphine, and concluded that these two formulations are equivalent in terms of analgesic effect and incidence of adverse events, when used as around-the-clock opioids (38). The same result has been demonstrated in a double-blind, randomized controlled trial comparing immediate- and sustained-release oxycodone (51).

Although available evidence suggests that either immediate-release or sustained-release opioids can be used as around-the-clock opioids, patients with severe or unstable pain were excluded from these studies. The panel has agreed that either immediate-release or sustained-release opioids may be used as around-the-clock opioids in patients with mild-to-moderate stable pain, and a rapid titration with immediate-release opioids or parenteral opioids is desirable in patients with severe or unstable pain.

(iv) Patients should be carefully assessed and observed for nausea/vomiting during opioid therapy and antiemetics should be readily available whenever nausea/vomiting occurs. [1C]

Because there are, to date, no clinical trials evaluating the efficacy of prophylactic antiemetics against opioid-induced nausea/vomiting, current evidence of prophylactic antiemetic use remains insufficient.

On the basis of panel consensus, this guideline recommends that patients should be observed carefully for the development of nausea/vomiting during opioid therapy, and that antiemetics should be prescribed as required when nausea/vomiting occurs. Once opioid-induced nausea/vomiting develops, antiemetics should be continued for 1 to 2 weeks because tolerance to opioid-induced nausea/vomiting may develop within 1 to 2 weeks after initiating opioid therapy.

The type of antiemetic can be chosen from dopamine antagonists (e.g. haloperidol, prochlorperazine), gastrointestinal prokinetic agents (e.g. metoclopramide) or antihistamine drugs.

(v) Patients should be carefully assessed and observed for constipation during opioid therapy; moreover, they should be provided with instructions regarding adequate fluid intake, diet and laxatives for the prevention of constipation. [1C]

To date, there have been no clinical trials evaluating the efficacy of prophylactic laxative use for opioid-induced constipation. Despite insufficient evidence, on the basis of the panel consensus, this guideline recommends that patients should be carefully assessed and observed for constipation during opioid therapy, and that they should be provided with instructions regarding adequate fluid intake, diet, and laxatives as preventive measures against constipation, considering its high prevalence with chronic opioid therapy.

(vi) Nonopioid analgesics may be continued when opioids are introduced in patients with inadequate pain control by nonopioid analgesics. [2B]

A double-blind, randomized controlled trial demonstrated that the addition of ibuprofen to oxycodone/acetaminophen therapy provided significantly better analgesic effects compared with placebo in cancer patients with pain from bone metastasis (52). In addition, another small, double-blind, crossover, randomized controlled trial demonstrated that the addition of a diclofenac suppository to regular parenteral morphine therapy provided significantly better analgesic effects than placebo in cancer patients (53). Furthermore, another open-label, randomized controlled trial demonstrated that the addition of oral ketorolac to regular morphine therapy showed an insignificant but better analgesic effect compared with morphine only (54). In this trial, dose escalation of morphine was significantly slower, whereas the maximum morphine dose was significantly lower in the ketorolac group. Ketorolac use tended to decrease opioid-related constipation but increased gastric discomfort. Another small, randomized controlled trial demonstrated that compared with the addition of placebo, the addition of acetaminophen showed a small but significantly better analgesic effect in cancer patients administered opioids (55).

Available evidence suggests that the use of a nonopioid analgesic combined with an opioid is more effective than using an opioid alone, despite the possibility of increasing incidence of gastric discomfort. We have therefore concluded that in patients with inadequately controlled pain despite treatment with nonopioid analgesics, nonopioid analgesics may be continued when opioids are introduced.

PATIENTS WITH INADEQUATELY CONTROLLED PAIN DESPITE INITIAL OPIOID USE

(i) Nonopioid analgesics should be used concurrently with opioids in patients who experience continuous pain with regular opioid use. [1A]

As previously mentioned, four randomized controlled trials comparing the combined use of nonopioid analgesics and opioids with the use of opioids alone demonstrated the superiority of the combination in producing an analgesic effect (52–55).