

Factors contributing to a good death

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One-week Short-Term Life Review interview can improve spiritual well-being of terminally ill cancer patients

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Abstract

Purpose: The primary aim of this study was to assess the efficacy of the Short-Term Life Review on the spiritual well-being, as well as anxiety, depression, suffering, and happiness of terminally ill cancer patients.

Method: Thirty patients reviewed their lives in the first session and they confirmed the contents in the album based on the life review in the second session. Duration of the treatment was one week. Measurement instruments included Functional Assessment Chronic Illness Therapy-Spiritual (FACIT-Sp), Hospital Anxiety and Depression Scale (HADS), Numeric Rating Scales of Suffering (from 0 to 6) and Happiness (from 1 to 7).

Results: After the therapy, the mean FACIT-Sp scores increased from 16 ± 8.2 to 24 ± 7.1 , anxiety score significantly decreased from 6.8 ± 4.7 to 3.0 ± 2.2 , depression score significantly decreased from 10.2 ± 4.7 to 6.6 ± 4.1 , suffering score significantly decreased from 3.4 ± 1.9 to 1.8 ± 1.4 , and happiness score significantly increased from 4.6 ± 1.9 to 5.6 ± 1.6 . Total HADS scores significantly decreased from 17 ± 8.6 to 9.5 ± 5.4 .

Conclusion: The Short-Term Life Review is feasible and may be effective in improving the spiritual and psychosocial well-being of terminally ill cancer patients.

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Keywords: psychotherapy; Short-Term Life Review; terminally ill cancer patients; spiritual well-being

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Introduction

Terminally ill cancer patients often experience spiritual distress, such as that engendered by searching for a meaning or purpose in life, problems associated with relationships with familiar people, or religious problems, in addition to depression or anxiety. Until recently, there have been few interventions for these problems. This study describes an intervention to ameliorate spiritual distress in terminally ill cancer patients.

Butler [1] reported that the life review process is a mean of reintegration and can give new significance and meaning to an individual's life. It is defined as 'the progressive return to consciousness of prior experience, which can be re-evaluated with the intention of resolving and integrating past conflict, thereby giving new significance to one's life.' The elderly are often confronted with lone-

liness, anxiety, worry about near-future death, and low ability in performing activities of daily living (ADL), resulting in low self-esteem or depression. To cope with these psychological problems, life review interviews have been used. Previous studies have shown the effects of life review on depression [2,3], self-esteem [2], and life satisfaction [4].

For cancer patients, however, there are few empirical studies on the effects of life reviews. Ando *et al.* [5] reported the effects of structured life review intervention on spiritual well-beings in terminally ill cancer patients. This study involved four sessions once in a week and spiritual well-being was measured with a quality of life (QOL) questionnaire, SELT-M [6]. After the life review interview, the patients' mood, positive thinking, and spirituality significantly increased. However, this study encountered a feasibility problem: sample patients did not complete the four sessions. At the

Table 1. Patient backgrounds

Primary tumor site		Gender
Lung	<i>n</i> = 8	Male (<i>n</i> = 8)
Stomach	5	Female (<i>n</i> = 22)
Pancreas	2	Age
Gallbladder	2	Mean age: 74 (total SD = 9.1)
Uterine	2	Marital states
Breast	1	Married (<i>n</i> = 29); widow (<i>n</i> = 11), widower (<i>n</i> = 3)
Kidney	1	Non-married (1)
Leukemia	1	Religion
Rectal	1	Christian (<i>n</i> = 4)
Tongue	1	Buddhism (<i>n</i> = 3), None (<i>n</i> = 22)
Colon	1	ECOG-PS
Mesothelioma	1	1 (<i>n</i> = 1), 2 (<i>n</i> = 3)
Myeloma	1	3 (<i>n</i> = 13), 4 (<i>n</i> = 13)
Lymphoma	1	Duration from the interview to patients' death
		Mean: 67 days

end of the study, the physical conditions of 9 of the 21 patients (about 30%) extremely deteriorated and failed to complete the psychotherapy process. Although structured life review may be effective in improving the spiritual well-being of terminally ill cancer patients, the long sessions decrease the feasibility; thus, we need a shorter version of life review therapy.

Dignity psychotherapy is a therapy for terminally ill cancer patients with shorter session time [7]. This involves only two or three sessions. Dignity is defined as 'quality or state of being worth, honored, or estimated' [8], and this therapy helps patients maintain their dignity. Patients review their lives with the aid of routine questions and the session is recorded, edited, and transcribed. In 2 or 3 days after, there is another session. The therapist reads the transcription to the patients, who give comments and make revisions. Patients reported a heightened sense of dignity, a sense of purpose, a sense of meaning, an increased will to live, and a decrease in distress. This study suggests the possibility that the life review interview is effective even for a short term.

We propose a new psychotherapy—the Short-Term Life Review—with short sessions for terminally ill cancer patients. Although there are at least four sessions in the structured life review to review a patient's life along developmental stages [9], Short-Term Life Review involves only two sessions. In the first session, patients review their lives, and the review is then recorded and edited. The therapist makes an album after the first session. In the second session, the patient and therapist view the album, and confirm the contents with appreciation.

The primary aim of this study was to assess the efficacy of the Short-Term Life Review on the spiritual well-being, as well as anxiety, depression, sufferings, and happiness, or terminally ill cancer patients.

Material and method

Participants

The subjects were cancer patients from the palliative care unit of two general hospitals and one home-care clinic. The inclusion criteria for this study were (1) patients with incurable cancer; (2) patients without cognitive impairment; (3) patients 20 years of age or older; and (4) patients for whom the primary physicians agreed would benefit from the psychological interventions. During the 11-month-study period, 35 patients were recruited through primary physicians. Table 1 shows the patients' background.

Interventions

Ethical aspect of this study was validated by both the board and the ethical committee of St. Mary's Hospital and St. Mary's College.

The Short-Term Life Review has two parts. In the first part, patients review their lives, and in the second, they re-evaluate, re-construct, and appreciate their life. The interviewer was a clinical psychologist (therapist). The interview procedure was based on a structured life review interview that was conducted individually, and the patient was asked to re-evaluate both good and bad memories. Question items were mainly based on the structured life review; however, they were not along developmental stages, and some items from Chochinov *et al.* [7] were added. The following questions were asked in the reviewing session: (1) What is the most important thing in your life and why? (2) What are the most impressive memories in your life? (3) In your life, what was the event that or the person who affected you the most? (4) What is the most important role in your life? (5) Which is the proudest moment of your life? (6) Is there anything about you that your family would need to

know, are there things you would want them to tell you, and, if possible, are there things you would want them to remember? (7) What advice or word of guidance would you wish to pass on to the important people in your life or to the younger generation?

The patient's narratives were recorded, and the therapist tried to listen to each word uttered by the patient. After the first session, the interview was first transcribed verbatim and the therapist made the album. To make the album, (1) key words in the answer to each question were selected. Words or phrases used by the patient were written in the album as often as possible; both good and bad things were included and feelings or re-framed thoughts—how he feels now—were written in the album. (2) The therapist pasted photos or drawings from various books or magazines that were related to the patients' words or phrases, to make the album more beautiful and more memory provoking. It took a week for the treatment.

Outcome measurements

To measure the effects of the Short-Term Life Review, we used the Japanese version of Functional Assessment Chronic Illness Therapy-Spiritual (FACIT-Sp) [10]. The validity and reliability of the FACIT-Sp Japanese version is well established [11]. Secondary end-points were anxiety, depression, suffering, and happiness. Anxiety and depression were measured by the Japanese version of the Hospital Anxiety and Depression Scale (HADS) [12,13]. Further, we used numeric rating scale about suffering (0–6) and happiness (1–7) [14] to compare the effects of the Short-Term Life Review with that of Dignity Psychotherapy by Chochinov *et al.* [7].

Statistical analysis

To evaluate the efficacy of the Short-Term Life Review in improving the patients' spiritual well-being, the Wilcoxon signed rank test was conducted on all scores of each scale before and after the Short-Term Life Review. Correlation analysis was used to examine the relationships between spiritual well-being and other variables. For intention-to-treat analyses, we additionally calculated the treatment effects using all patient data by the last observation carried forward methods.

Results

Five of the patients were excluded from this study because of unexpected deterioration in health. Thus, a total of 30 patients completed all sessions. Two patients' consciousness level decreased due to disease progression, one had severe and uncontrollable pain, one developed pneumonia, and one lost motivation to participate because of decreasing ADL.

Table 2 shows average and standard deviation scores. After the Short-Term Life Review, the mean FACIT-Sp scores increased from 16 ± 8.2 to 24 ± 7.1 ($Z = -4.2, P = 0.001$), the anxiety score significantly decreased from 6.8 ± 4.7 to 3.0 ± 2.2 ($Z = -3.8, P = 0.001$), the depression score significantly decreased from 10.2 ± 4.7 to 6.6 ± 4.1 ($Z = -3.7, P = 0.001$), the suffering score significantly decreased from 3.4 ± 1.9 to 1.8 ± 1.4 ($Z = -3.5, P = 0.001$), and the happiness score significantly increased from 4.6 ± 1.9 to 5.6 ± 1.6 ($Z = -3.2, P = 0.002$). Total HADS scores significantly decreased from 17 ± 8.6 to 9.5 ± 5.4 ($Z = -4.1, P < 0.001$).

Those changes remained statistically significant using the intention to treat analysis: The mean FACIT-Sp scores significantly increased from 16 ± 7.8 to 23 ± 7.1 ($Z = -4.2, P = 0.001$), the anxiety score significantly decreased from 7.0 ± 4.8 to 3.7 ± 3.4 ($Z = -3.8, P = 0.001$), the depression score significantly decreased from 10.4 ± 4.6 to 7.2 ± 4.4 ($Z = -3.7, P = 0.001$), the suffering score significantly decreased from 3.5 ± 1.8 to 2.1 ± 1.5 ($Z = -3.5, P = 0.001$), and the happiness score significantly increased from 4.5 ± 1.9 to 5.3 ± 1.7 ($Z = -3.2, P = 0.002$). Total HADS scores significantly decreased from 17 ± 8.6 to 11 ± 6.8 ($Z = -4.1, P < .001$).

As shown in Table 3, the FACIT-Sp significantly correlated with anxiety ($r = -0.37$), depression ($r = -0.76$), total HADS ($r = -0.73$), sufferings ($r = -0.70$), and happiness ($r = 0.57$).

Discussion

Effects of Short-Term Life Review

The first important finding is beneficial effect of the Short-Term Life Review on spiritual well-being in terminally ill cancer patients. The fact that the FACIT-Sp scores significantly increased after the Short-Term Life Review shows the effect of this

Table 2. Changes in outcome measures

	FACIT-SP	Anxiety	Depression	Total HADS	Sufferings	Happiness
Before	16 ± 8.2	6.8 ± 4.7	10.2 ± 4.7	17 ± 8.6	3.4 ± 1.9	4.6 ± 1.9
After	24 ± 7.1	3.0 ± 2.2	6.6 ± 4.1	9.5 ± 5.4	1.8 ± 1.4	5.6 ± 1.6
P value	$Z = -4.2,$ $P = 0.001$	$Z = -3.8,$ $P = 0.001$	$Z = -3.7,$ $P = 0.001$	$Z = -4.1,$ $P = 0.001$	$Z = -3.5,$ $P = 0.001$	$Z = -3.2,$ $P = 0.002$

Table 3. Correlation coefficients among variables at the post Short-Term Life Review

	FACIT-Sp	Anxiety	Depression	Total HADS	Sufferings	Happiness
FACIT-Sp	1.0					
Anxiety	-0.37*	1.0				
Depression	-0.76**	0.41*	1.0			
Total HADS	-0.73**			1.0		
Sufferings	-0.70**	0.47*	0.73**	0.75**	1.0	
Happiness	0.57**	-0.27	-0.57**	-0.55**	-0.47**	1.0

* $P < 0.05$, ** $P < 0.01$.

therapy on spiritual well-being of cancer patients. Regarding the secondary endpoint, there were significant differences between pre- and post-intervention scores for anxiety, depression, suffering, and happiness.

Why does the Short-Term Life Review affect these variables? The following considerations may be relevant: (1) a patient can express emotion or distress without being concerned about the feelings of family or others. Most Japanese prefer not to give burden to family or friends. Moreover, in the sessions, there is ample time for patients to discuss anything they wish to mention, sometimes in an informal manner. This is related to psychological purification. (2) Patients can confirm their acquisitions or roles in life, narrating their lives as they have lived them, and can re-evaluate both good and bad memories with emotional support from the therapist. (3) Patients can view, touch, and appreciate their own album. Through these processes, patients find meaning in life and re-evaluate it, and their spiritual well-being increases. This results in a decrease in anxiety, depression, and suffering and an increase in happiness.

Adapting these processes with the previous theoretical model [15,16], we can explain the effects of Short-Term Life Review. A patient has a purpose or a goal for his life when he is healthy. However, when he falls into serious illness, it is often difficult for him to attain his purpose or a goal because of unexpected serious illness, and he feels much distress. In this situation, when he receives the Short-Term Life Review, he can re-think and modifies his original purpose or goals into attainable ones, he feels a positive mood. Short-Term Life Review may contribute for a patient to reconstruct his life being congruent with cancer in his life.

Feasibility

It would be remarkable for Short-Term Life Review to have high feasibility. The percentage of patients deteriorating with this therapy was only 17%, although in the previous study [5] it was 30% for patients using the Structured Life Review. We describe some factors related to feasibility. (1) The Short-Term Life Review is completed in a week, and this short-term intervention enables terminally ill cancer patients to complete an intervention. (2)

Patients with very low functionality in ADL can participate because the patients review their lives while lying on bed. Both problem-solving therapy for cancer patients [17] and cognitive behavior therapy for cancer patients [18] have proved to be effective. However, patients need some level of ADL; they may plan their schedule and conduct and evaluate their behavior or cognition. It may be difficult to conduct interventions for terminally ill cancer patients with much lower ADL. Moreover, the effects of these psychotherapies on spiritual well-being have not been evaluated. To manage spiritual distress, there is meaning-centered group psychotherapy [19], in which groups of patients talk about the meaning or purpose of life over a period of 8 weeks. However, it may be very difficult for terminally ill cancer patients with performance status of 3 or 4 to reach the end of this therapy and to travel to the places where the group sessions are held. In comparison with these previous studies, the present findings suggest that the Short-Term Life Review can be more feasible. Moreover, the procedures used in this therapy are clearly defined and medical personnel other than psychotherapists may be able to conduct it in various situations.

The following is the one of the cases. When a therapist began the session at the patient's bedside, a patient became emotional and covered his eyes while narrating his story. The therapist tried to be a therapeutic listener. The patient had never expressed his emotions in front of his family; however, he could readily express his emotions and feelings in the sessions. He was able to describe his suffering and his regret that he would die in the near future. He had worked as a gardener for a long time. It was very hard to become a gardener. There had been some failures when he was running his own small company, and he had worked hard. He described his life with his family, particularly his children, who were under 20 years old. After the first session, the therapist made an album for the patient. In the second session, the therapist and patient talked about the album and looked at it together. The patient listened to the therapist and became emotional. The therapist prompted the patient to re-evaluate both his good and bad memories by asking him to reconstruct his life, with questions like 'How do you recognize that memory now?' and 'how do you feel now?' The

One-week Short-Term Life Review interview

patient wanted to live much longer, but had to reconstruct and integrate his life in a short time. He seemed to be satisfied that he was able to leave the park gardens, which many people are presently enjoying. He also expressed gratitude to his family and friends. He said 'These sessions were very helpful for me to set my memories in place.'

Comparison of Short-Term Life Review with Dignity Psychotherapy

There are both similarities and differences in methods between Short-Term Life Review and Dignity Psychotherapy. In both studies, patients review their lives for one time and there are some common questions. However, there are some differences between them. (1) In Dignity Psychotherapy, patients are offered the opportunity to address issues that matter the most to them or to speak of things they wish to remember the most as death draws near. In the Short-Term Life Review, the therapist does not intentionally prompt the patient to speak about the aftermath. (2) In the Short-Term Life Review, the therapist prompts the patient to review both good and bad memories to re-evaluate the bad memories and integrate them for patients' themselves; in Dignity Psychotherapy, however, bad memories or bad things are sometimes omitted from the transcript, because the transcript is for both the patient and his family. (3) In Dignity Psychotherapy, the therapist and the patient image something like an album in the second session, whereas in the Short-Term Life Review the therapist makes a small album based on the transcript after first session and both the patient and the therapists view the album together and the therapist promotes the patients to appreciate and re-evaluate their lives during the second session.

To compare the effects of the two therapies, we asked some common questions such as 'Are there anything that you would want your family to know about you, and are there things you would want them to tell?' In Dignity Therapy, the transcript is intended for those left behind. However, few patients answered this question and mentioned inheritance in the present study. There may be some cultural differences among patients. In future studies, we will select questions tailor made for each patient based on cultural differences.

Limitation

Finally, we mention the limitations of this study. First, there was no control group to enable us to assess the effects of this therapy because the terminally ill patients in this study were in a very serious physical and mental state and we could not burden them by asking questions that did not

contribute directly to their QOL. Second, the statistical significance in the measurement outcomes does not directly mean clinical significance. We were unable to conclude the clinical significance of this intervention due to the lack of established cut-off points of the FACIT-Sp. Third, almost all patients in this study were in palliative care ward or hospice care clinic, and the generalization of the findings to other situations cannot be automatically supported. Randomized controlled trial is promising to confirm the treatment benefits of the Short-Term Life Review interview.

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Measuring the regret of bereaved family members regarding the decision to admit cancer patients to palliative care units

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Abstract

Objective: The purposes of this study were to develop a bereaved family regret scale measuring decision-related regret of family members about the admission of cancer patients to palliative care units (PCUs) and to examine the validity and reliability of this scale.

Method: Bereaved families of cancer patients who had died in one regional cancer center from September 2004 to February 2006 received a cross-sectional questionnaire by mail. The questionnaire contained seven items pertaining to decision-related regret about the patient's admission to the PCU, the Care Evaluation Scale (CES), an overall care satisfaction scale, and a health-related quality-of-life (QOL) scale (SF-8). One month after receiving a completed questionnaire, we conducted a retest with the respondent.

Results: Of the 216 questionnaires successfully mailed to the bereaved families, we received 137 questionnaires and were able to analyze the responses for 127 of them, as the other 10 had missing data. By exploratory factor analysis and confirmatory factor analysis, we identified two key factors: intrusive thoughts of regret and decisional regret. This scale had sufficient convergent validity with CES, overall care satisfaction, SF-8, sufficient internal consistency, and acceptable test-retest reliability.

Conclusion: We have developed and validated a new regret scale for bereaved family members, which can measure their intensity of regret and their self-evaluation about their decision to admit their loved ones to PCUs.

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Introduction

Researchers into end-of-life issues have recognized the value of what they have called a 'good death'. Critical to achieving a 'good death' is the 'completion of life,' which entails one's being prepared for dying, a feeling that one's life has been completed, no regrets about one's death, and family members who also have no regrets about one's death. Thus, minimizing the regret of cancer patients and their families is an important issue for achieving a 'good death' [1, 2]. However, bereaved

family members who have lost a loved one may find themselves experiencing self-blame feelings of regret along the lines of, 'I may have had to do it for my loved one' or 'I may not have had to do it for my loved one' [3].

Such feelings are a component of regret, the painful sensation that can result from recognizing that 'what is' compares unfavorably with 'what might have been' [4]. Early regret studies have found that a bad outcome resulting from action seemed more regrettable than the same bad outcome resulting from inaction [5] and that regretta-

ble feelings may exhibit a temporal reversal, with action evoking more regret in the short term and inaction evoking more regret in the longer term [6]. Subsequent research has categorized regrets in the daily decision context into three types according to their target: outcome regret, option regret, and process regret [7]. For each of these regret types, researchers have examined the effects of anticipated regret on decision-making as well as the effect of decision-making on experienced regret. Investigators have explored various theories and models to try to explain decision-related regret. Connolly and Zeelenberg, for instance, have recently proposed a new model called decision justification theory (DJT) [8]. DJT postulates two core components of decision-related regret: evaluation of the outcome and the feeling of self-blame for having made a poor choice. The overall feeling of regret at the decision is the combination of these two components. Thus DJT might offer a new explanation as to how people still feel regret even when they experience a situation in which the actual outcome is good. In contrast, most regret studies to date have evaluated regret by examining either the past decision or the self-blame feeling.

With respect to cancer patients, regret studies have typically focused on fatal decisions regarding what course of treatment to follow, e.g. [9] or whether to undergo a screening test [10]. Several studies of prostate cancer patients have established that patients can feel substantial regret following their cancer-related fatal decisions [11–13] and that such treatment-related regret is associated with worse current health-related quality of life (QOL) [11] and with worse quality of life and emotional well-being [12]. Future research should further explore how aspects of the fatal decision process affect later regret in cancer patients and their families.

Family members will face various decisions as well as the cancer patients themselves during the course of illness. However, no reports are available regarding decision-related irretrievable regret among family members within bereaved families. Cohesiveness and control are much greater within Japanese than within western families [14]. Also, the opinions of family members tend to exert greater influence on clinical decision-making in Japan than in the United States [15, 16]. The assessment of current irretrievable regret can retrospectively color past decision-making processes. Current irretrievable regret also can strongly affect future psychological status. Developing a vigilant decision-making model focused on the regret of bereaved family could help provide useful information for improving decision-making by cancer patients and their families. One important area of decision-making for cancer patients and their families involves the decision process by which physicians

initially refer patients to palliative care units (PCUs) [17]. This study thus endeavored to develop a bereaved family regret scale measuring irretrievable regret regarding the decision to admit cancer patients into PCUs and to examine the validity and reliability of this scale.

Methods

Participants and procedure

Our initial set of potential study participants comprised family members of patients who had died from September 2004 to February 2006 in Ibaraki prefecture, Japan. Inclusion criteria were as follows: the patient had died in a PCU; the patient was 20 years of age or older; and the patient had been admitted to the PCU at least three days prior to death. Exclusion criteria were as follows: the family member participant had already been recruited for another questionnaire survey for bereaved family members; the family member's primary physician determined that the participant would suffer serious psychological distress from participation in the study; the patient's cause of death was either directly treatment related or secondary to a treatment-related injury; or no member of the bereaved family was 20 years of age or older, capable of replying to a self-reported questionnaire, or aware of the patient's diagnosis of malignancy.

We mailed questionnaires to potential respondents in October 2006 and mailed reminders in November 2006 to those who had not responded. We asked respondents who did not wish to participate in the survey to indicate that they did not wish to participate and to return the questionnaire. To examine test-retest reliability, we sent a follow-up questionnaire one month after we received a completed questionnaire. The institutional review boards of Tsukuba Medical Center Hospital approved the ethical and scientific validity of this study.

Of the 224 questionnaires sent to eligible bereaved families, eight were undeliverable. We received 137 of the remaining 216 questionnaires, among which we had to exclude 10 due to missing data. Thus, we analyzed 127 responses (effective response rate, 59%). Among these 127 respondents who submitted analyzable test questionnaires, we sent retest questionnaires to the 121 bereaved families who responded during the study period; the other six families submitted their test responses too late to be included in the retest program. We received 82 retest questionnaires, among which we excluded 11 due to missing data. In total, we analyzed 71 retest questionnaires (effective response rate, 59%).

Measuring the decision-related regret of bereaved family

Measures

Decision-related regret about admission to PCUs

The questionnaires asked participants to rate on a 5-point self-reported Likert scale (strongly disagree–strongly agree) their level of agreement with each of seven possible regrets that they may have experienced regarding their decision-making in the past about admitting their loved ones to a PCU. Most previous studies have evaluated regret only for single statements, such as ‘how do you feel regret concerning XX’. In addition, we collected from prior studies three statements measuring the evaluation of decisions in the past [11, 18] and three other statements measuring severity and intensity of regret [19]. The evaluation-of-decision statements included, ‘I made the right decision’ and ‘I would make the same decision if I had to do it again’. The severity and intensity of regret statements included, ‘Once I start thinking about possible outcomes had I made a different decision, I find it difficult to think about other matters’ and ‘I had difficulty concentrating on daily activities because thoughts about regret kept entering my mind’. We constructed the wording of these statements based upon the palliative physicians’ and psychologists’ comments regarding understandability and wording.

Care evaluation scale, short version

We used the Care Evaluation Scale (CES), short version, to examine concurrent validity [20]. The questionnaire design has the respondent evaluating the necessity of improvement for each item on a 6-point Likert scale (improvement is not necessary–highly necessary). The short version of CES used in this study comprises 10 items covering the following 10 domains: help with decision-making for patient, help with decision-making for family, physical care by physician, physical care by nurse, psycho-existential care, environment, cost, availability, coordination of care, and family burden.

Overall care satisfaction

We assessed overall care satisfaction as part of our examination of concurrent validity by asking the following question, developed in a previous study [21]: ‘Overall, were you satisfied with the care provided in the hospital?’ The participant again responded on a 6-point Likert scale.

Health-related QOL

We used the SF-8 Japanese version [22], the short form, which is derived from the health-related QOL scale called the MOS 36-Item Short Form Health survey (SF-36). The eight items cover the eight concepts measured by the SF-36 (one item per concept), using a 5- or 6-point Likert scale. The

SF-8 provides two summary scores for physical and mental health: a Physical Component Scale and a Mental Component Scale. Scores for each item and summary measurements range from 0 to 100, with higher scores indicating better health. This scale includes questions such as the following: ‘Overall, how would you rate your health during the past 4 weeks’; ‘During the past 4 weeks, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)’; and ‘During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?’

Participant characteristics

We extracted information concerning the patient’s age, sex, and hospital days from a medical database. We asked the respondent bereaved family members to provide the following personal information about themselves: age, sex, health status during caregiving period, relationship with patient, frequency of attending the patient, presence of other caregivers, living status with patient, faith, education, and household income during the caregiving period.

Analysis

We utilized the Statistical Package for SPSS for Windows (Version 14.0) for all data analyses. To examine validity of our regret scale, we conducted an exploratory and a confirmatory factor analysis along with correlation analyses of our regret scale vs CES, overall satisfaction, and QOL. To examine the reliability of the regret scale, we assessed the internal reliability of its two subscales with Cronbach’s α coefficients. We used correlation coefficients to assess test–retest reliability.

Results

Characteristics of participants

Table 1 shows the demographic characteristics of the 127 participants included in the development analysis. We compared the demographic characteristics of these 127 participants with those of the 71 participants included in the validation analysis. We identified no significant differences between the two groups with respect to all demographic characteristics. Table 1 also shows descriptive statistics of decision-related regret, CES, overall satisfaction, and health-related QOL.

Validity

All of the seven items had a moderate degree of variance, and no item evidenced bias. Using these

Table 1. Characteristics of the bereaved family and patient

	N = 127 Patient numbers or mean \pm SD	%
<i>Bereaved family</i>		
Age	55.85 \pm 12.11	
Sex, male	44	34.6
<i>Health status during caregiving period</i>		
Good	33	26
Somewhat good	71	55.9
Bad	20	15.7
Strongly bad	2	1.6
<i>Relationship to patient</i>		
Spouse	61	48
Parent	42	33.1
Parent-in-law	13	10.2
Others	10	7.9
<i>Frequency of attending patient</i>		
Everyday	96	75.6
4–6 days/week	11	8.7
1–3 days/week	15	11.8
None	3	2.4
<i>Presence of other caregivers</i>		
Living with patient	106	83.5
<i>Education</i>		
Less than high school	17	13.4
High school	56	44.1
Some college	28	22
Postgraduate	25	19.7
<i>Household income during caregiving period</i>		
Less than 250	13	10.2
250–500	58	45.7
500–750	25	19.7
750–1000	14	11
More than 1000	14	11
Care Evaluation Scale	75.49 \pm 17.63	
Overall satisfaction	4.76 \pm 0.96	
SF8; Physical Component Scale	48.78 \pm 7.81	
SF8; Mental Component Scale	48.52 \pm 6.37	
<i>Patient</i>		
Age	68.12 \pm 12.28	
Sex, male	68	53.5
Hospital days	41.63 \pm 33.90	

seven items, we conducted an exploratory factor analysis with promax rotation and the maximum-likelihood method. A minimal eigenvalue >1 yielded a 2-factor solution (Table 2), in which these two factors explained 74% of the variance. The correlation coefficient between the two factors was 0.32 ($p < 0.01$). Factor 1, which measured the degree of focus on regret, we named 'intrusive thoughts of regret'; factor 2, which measured evaluation of decision-making in the past, we named 'decisional regret.'

Then, to confirm the adequacy of the scale structures, we conducted a confirmatory factor analysis with these seven items. The results

indicated that item 3 was the item with highest factor loadings for both factors 1 and 2. We then constructed two models, shown in Figure 1, and compared the fit indexes of the two models. We adopted model 2 because its fit index was higher than that of model 1.

Table 3 contains the Pearson correlation coefficients showing the correlation between the scores of regret subscales and scores for CES, overall care satisfaction, and health-related QOL. As expected, the scores for CES and overall care satisfaction negatively correlated with each regret subscale. Physical QOL and mental QOL correlated with only the intrusive thoughts subscale.

Reliability

We assessed the internal reliability of the two subscales with Cronbach's α coefficients. Internal consistency was high for both 'intrusive thoughts of regret' ($\alpha = 0.85$) and 'decisional regret' ($\alpha = 0.79$) subscales. We then defined the sums for each sub-factor as the intrusive thoughts of regret score and the decisional regret feeling score, respectively. Using these scores, we assessed test-retest reliability using correlation coefficients. Among the 71 participants who responded in both surveys, correlation coefficients among subscales were moderately high for factor 1 ($r = 0.69$, $p < 0.01$) and factor 2 ($r = 0.70$, $p < 0.01$).

Discussion

The purpose of this study was to develop a PCU's admission-related regret scale for the bereaved family and to identify its validity and reliability. Among the bereaved families, decisional-related regret was irretrievable. Furthermore, most families had thought that their past decision was fatal for the patients. By exploratory factor analysis and confirmatory factor analysis, we identified two key factors: intrusive thoughts of regret and decisional regret. This study provided good evidence of the reliability and validity of these two factors within this Japanese population. Using these two factors, we developed a new regret scale for bereaved family members, which was able to measure their intensity of regret and their self-evaluation about their decision to admit their loved ones to PCUs. Since this regret scale contains a small number of items and a simple structure, the scale is open to broad use.

We were able to delineate the structure of our two factors, intrusive thoughts of regret and decisional regret. These two factors appear to correspond to the two core components of DJT (intensity of regret and their self-evaluation) [8]: Intrusive thoughts of regret correspond to intensity of self-blame feelings, and decisional regret corre-

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Table 2. Results of exploratory factor analysis

Items	Mean ± SD	Factor loadings		Communality
		F1	F2	
Once I start thinking about possible outcomes had I made a different decision, I find it difficult to think about other matters (v6)	1.88 ± 1.15	0.90	0.22	0.67
I had difficulty concentrating on daily activities because thoughts about regret kept entering my mind (v7)	1.72 ± 1.10	0.83	0.18	0.62
I could not stop thinking that the situation might have changed if I had made a different decision (v5)	2.03 ± 1.16	0.81	0.33	0.59
It was the right decision (v1*)	1.63 ± 0.75	0.30	0.99	0.82
I would make the same decision if I had to do it again (v2*)	1.73 ± 0.90	0.25	0.89	0.79
I regret the decision that was made (v3)	1.69 ± 0.08	0.56	0.57	0.48
I am satisfied with the decision (v4*)	2.06 ± 1.04	0.12	0.49	0.26

*Reversed item.

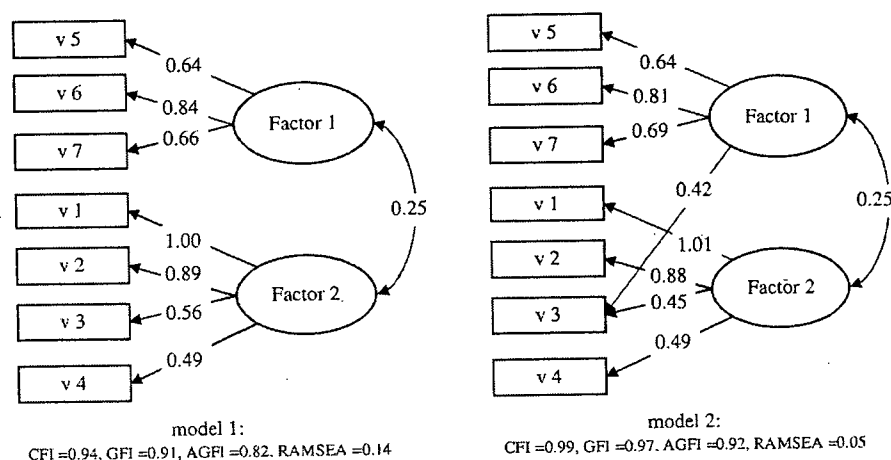


Figure 1. The results of confirmatory factor analysis and fit indices

Table 3. Criterion validity as measured by Pearson correlations

Scales	CES	Overall care satisfaction	Physical QOL	Mental QOL
F1: intrusive thoughts about regret	-0.33**	-0.33**	-0.22*	-0.37**
F2: decisional regret	-0.27**	-0.46**	-0.08	-0.09

* $p < 0.05$, ** $p < 0.01$.

sponds to evaluation of decision-making and subsequent outcome. Each of the two factors contained four of the seven statements; one statement overlapped both factors. The overlapping statement, 'I regret the decision that was made', directly represented the overall regret of bereaved family members about their decision-making. Our regret scale could thereby measure three aspects of the bereaved families' regret: overall degree of regret, evaluation of decisional regret, and severity of intrusive thoughts about regret. Evaluation of the details of regret assists greatly in formulating an appropriate plan of regret management and therapy. Several recent studies have examined regret management and therapy for cancer patients [23,24]. However, to develop better evidence-based regret management or regret therapy, future research should explore the effects of

the decision-making process or options on subsequent irretrievable regrets. We believe that psychosocial theories such as reference comparisons theory or justifications theory can provide a basis for utilizing our new scale to establish effective regret management and therapy.

We found good evidence for the reliability and validity of our regret scale. Examination of the convergent validity of this scale determined that the score of CES and overall satisfaction negatively correlated with each regret subscale, indicating that this regret scale could adequately measure regrets regarding decision-making about admission to PCUs. On the other hand, both physical and mental QOL scores did not correlate with decisional regret but correlated only with intrusive thoughts of regret. This pair of findings indicates that the bereaved family's QOL is not influenced by

how much they regret their decision but rather by how often their regretful thoughts come to mind. The finding that intrusive thoughts of regret were associated with health-related QOL is in accord with the results of previous studies among adults [25]. We believe that decisional regret and intrusive thoughts of regret comprise different concepts and thus should be measured separately. Our findings suggest that intrusive thoughts of regret have the potential to affect the health-related QOL of bereaved family members.

One limitation of our study is the somewhat small sample size of our study, especially for the retest survey. We sent out retest questionnaires one month after we received a completed questionnaire. Although our study design assumed that the regret of the bereaved family did not change during this one-month period, empirical confirmation of this assumption is lacking. Our analysis of test-retest reliability yielded correlation coefficients among subscales that were moderately high.

Utilizing this new scale to assess the regret of the bereaved family should help clinicians evaluate decision-making about the admission of cancer patients into PCUs retrospectively. Use of this scale in multi-institutional outcome surveys should assist evaluation of quality differences between institutions in the decision-making process. Developing a vigilant decision-making model of cancer patients and their families and examining the association of this model with irremediable regret will require future studies in order to provide useful information about decision-making aids. Our new scale thus represents the first step for these future studies.

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ORIGINAL ARTICLES

Unexpectedly high prevalence of akathisia in cancer patients

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ABSTRACT

Objectives: Complications of neuropsychiatric disorders are often detected in cancer patients. Adjustment disorders, depression, or delirium are common psychiatric disorders in these patients, and drug-induced neuropsychiatric problems are sometimes referred for psychiatric consultation. Prochlorperazine and other antiemetic drugs that are phenothiazine derivatives are also reported to cause akathisia due to the blockade of the dopamine receptor in the central nervous system, but the prevalence of akathisia in patients undergoing cancer treatment has not been reported. This study seeks to explore the prevalence of such drug-induced syndromes (e.g., akathisia) in this population.

Methods: This present study was a prospective study. The subjects of this study were 483 consecutive patients with cancer who had been referred to the Department of Psychiatry in Kanagawa Prefecture Cancer Center from February 1, 2004, to November 30, 2005. Trained psychiatrists conducted a nonstructured psychiatric interview and neurologic examination to establish psychiatric diagnoses according to DSM-IV and the presence or absence of drug-induced extra pyramidal symptoms. The past and current medications used in their cancer treatment were also examined in detail for an accurate evaluation.

Results: A psychiatric diagnosis was made in 420 (87.0%) of the 483 cancer patients examined, and akathisia, a drug-induced movement disorder, was unexpectedly prevalent among the patients; 20 of 420 (4.8%) patients had developed akathisia from an antiemetic drug, prochlorperazine.

Significance of results: Diagnosing such adverse drug reactions may be difficult due to complicating factors in cancer treatment, and the inner restlessness observed in akathisia is likely to be regarded as a symptom of a primary psychiatric disorder. The authors suggest that oncologists should optimize the use of antiemetic drugs and be aware of akathisia as a possible complication of cancer treatment.

KEYWORDS: Adverse drug reaction, Akathisia, Cancer, Prochlorperazine, Psychiatric referral

INTRODUCTION

Neuropsychiatric disorders are often observed in cancer patients. In an initial study, Derogatis et al. (1983) reported that a psychiatric diagnosis was made in 47% of cancer patients, and adjustment disorders were the most frequent (68%), followed by depression (13%) and delirium (8%). A recent Japanese study of 1721 psychiatric referrals at a cancer center revealed that the most frequent psychiatric diagnoses, which were made according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV; American Psychiatric Association, 1994), were adjustment disorders, followed by delirium, major depression, dementia, and schizophrenia (Akechi et al., 2001). Among the psychiatric referrals, neuropsychiatric conditions associated with adverse drug reactions are sometimes detected. These conditions are sometimes difficult to diagnose because of multiple complicating factors in patients undergoing cancer treatment and oncologists' unfamiliarity of these conditions. Medication-induced movement disorders, a DSM-IV diagnostic category, are one of these conditions. This category includes neuroleptic-induced acute akathisia, neuroleptic malignant syndrome, and so on.

Akathisia is characterized by subjective feelings of restlessness accompanied by objective signs of motor restlessness such as fidgety movements of the legs and an inability to sit or stand still (American Psychiatric Association, 1994). Antiemetic drug-induced akathisia in cancer patients has been reported previously (Fleishman et al., 1994); a retrospective study confirmed that an antiemetic drug was one of the risk factors of akathisia in cancer patients (Gattera et al., 1994). But the incidence of akathisia among psychiatric referrals in a cancer center has not been published to date.

SUBJECTS AND METHODS

This present study was a prospective study. The subjects of this study were 483 patients (225 males, 258 females; mean age \pm SD = 58.9 \pm 13.5 years) with cancer who had been referred to the Department of Psychiatry in Kanagawa Prefecture Cancer Center from February 1, 2004 to November 30, 2005. The consultation was requested for psychiatric evaluation, diagnosis, and treatment. The prevalence of the various sites of cancer was as follows: head and neck, $n = 60$, 12.4%; lung, $n = 58$, 12.0%; breast, $n = 55$, 11.4%; leukemia, $n = 50$, 10.4%; stomach, $n = 35$, 7.2%; uterus, $n = 33$, 6.8%; rectum, $n = 21$, 4.3%; esophagus, $n = 20$, 4.1%; colon, $n = 19$, 3.9%; pancreas, $n = 18$, 3.7%; and others, $n = 114$, 23.6%.

The psychiatric interviews were consecutively conducted with the patients by well-trained psychiatrists. The past and current medications used in their cancer treatment were also examined in detail for an accurate evaluation. The psychiatric diagnoses were made according to DSM-IV.

This study was not referred to the ethics committee of the cancer center and informed consent was not obtained from the patients because psychiatric interview, assessment, and diagnosis were within our routine work and extraordinary burdens and intervention were not placed on these patients.

RESULTS

The prevalence of the various psychiatric diagnoses are listed in Table 1. A psychiatric diagnosis (axis I diagnosis of DSM-IV) was made in at least 420 of 483 cases (87.0%). Although the psychiatric diagnoses were diverse, the most frequent psychiatric diagnoses were adjustment disorders (30.2% of all subjects diagnosed) followed by depression (30.0%), and delirium (13.9%). Tied for fourth as most prevalent diagnoses were a medication-induced movement disorder (acute or tardive akathisia, 4.1%) and anxiety disorders (4.1%). Akathisia accounted for 4.8% of all psychiatric diagnoses. All patients with a movement disorder exhibited symptoms of akathisia, including a subjective feeling of restlessness and motor restlessness, such as an inability to sit and stand still. Half of these patients were diagnosed

Table 1. Psychiatric diagnoses (Axis I diagnosis of DSM-IV) in referred cancer patients

Psychiatric diagnosis	No. (N = 483)	Percent
Adjustment disorders	145	30.0
Mood disorders	124	25.7
Major depressive disorders	122	25.3
Bipolar disorder	2	0.4
Delirium	67	13.9
Medication-induced movement disorders	20	4.1
Anxiety disorders	20	4.1
Somatoform disorders	14	2.9
Schizophrenia and other psychotic disorders	11	2.3
Substance-related disorders	10	2.1
Dementia	9	1.9
Undetermined ^a	8	1.6
No diagnosis	55	11.4

^aEight patients were categorized as "undetermined" because of insufficient psychiatric interview time for a definitive diagnosis.

as having acute akathisia according to its onset after medication.

Table 2 shows the profiles of all the patients with akathisia (10 males and 10 females, mean age \pm SD: 54.5 ± 14.2 years). Except for only two cases, akathisia had not been diagnosed until the psychiatric referral; these patients were referred to the psycho-oncologist because of their mental state, such as restlessness, anxiety, agitation, and so forth. Akathisia was induced by an antiemetic drug, prochlorperazine, in 16 of 20 patients; 3 were given 10 mg, and 13 were given 15 mg of prochlorperazine daily. In three cases, haloperidol, an antipsychotic agent, induced the akathisia. The onset of akathisia varied from 1 day to 9 months after the dopamine antagonist was prescribed.

DISCUSSION

In this study, akathisia was the fourth most common psychiatric diagnosis among all the psychiatric referrals. In almost cases, the akathisia was induced by an antiemetic drug, prochlorperazine, which was

given for treating the nausea caused by morphine. Prochlorperazine is a phenothiazine derivative, and its antiemetic effect is due to its blockade of the central dopaminergic system; this dopaminergic blockade possibly causes extrapyramidal symptoms at the same time (O'Hara, 1958; Bateman et al., 1989). Prochlorperazine-induced akathisia in cancer patients has been reported previously. Fleishman et al. (1994) conducted a telephone interview of 24 cancer patients who had taken prochlorperazine and metoclopramide, another antiemetic drug, with chemotherapy and found that 50% of the patients had subjective motor restlessness. Gattera et al. (1994) determined risk factors of akathisia in terminally ill patients by a retrospective control study; exposure to haloperidol, prochlorperazine, promethazine, or morphine was a factor that predisposed patients to akathisia, respectively. Akathisia should be considered in patients to whom antiemetic drugs are administered, and in the present study, the authors prospectively examined the prevalence of neuropsychiatric complications in cancer patients and found an unexpectedly high prevalence of akathisia among

Table 2. Clinical characteristics of the 20 patients with akathisia

No.	Age	Sex	Cancer site	Reason for psychiatric referrals	Current prochlorperazine treatment	Current opioid treatment	Other dopamine blockers	Onset of akathisia after the start of medication (days)
1	51	M	neck	restlessness	15 mg	+		13
2	44	F	colon	bizarre behavior	15 mg	+		3
3	69	F	breast	anxiety	15 mg	+		1
4	82	F	uterus	loss of vigor	-	-	Haloperidol 1.5 mg	1
5	63	M	stomach	irritability, restlessness	15 mg	+		30
6	46	F	small intestine	restlessness	15 mg	+		33
7	39	M	lung	anxiety, insomnia	15 mg	+		58
8	57	F	breast	severe mental illness	15 mg	+		7
9	27	M	stomach	restlessness	10 mg	+		14
10	57	F	lung	depressive state	15 mg	+		30
11	46	F	bone	restlessness	15 mg	+		93
12	60	F	others	restlessness	15 mg	+		285
13	57	M	lung	restlessness	15 mg	+		97
14	66	M	esophagus	agitation	-	-	Haloperidol 5 mg	2
15	71	M	pancreas	restlessness	15 mg	+		17
16	72	M	stomach	anxiety	10 mg	+		31
17	50	M	colon	inability to sit	10 mg	+		36
18	40	M	myeloma	anxiety	-	+	Chlorpromazine 10 mg	3
19	58	F	lung	restlessness	15 mg	+		28
20	32	F	leukemia	agitation	-	+	Haloperidol 5 mg	12

patients. Prior to the referrals, only two oncologists had suspected akathisia. They referred the patients because of "unexpected behavioral changes," "bizarre behavior," and so on, and therefore asked for a psychiatric evaluation.

Whereas the first, second, and third most common psychiatric disorders observed in cancer patients referred for psychiatric evaluation were consistent with observations in previous studies, akathisia was more frequent in our study compared to previous ones (Massie & Holland, 1987; Grassi et al., 2000; Akechi et al., 2001). It is not clear why there are differences in the prevalence of various psychiatric diagnoses among the studies. Were most of the cases of akathisia overlooked or misdiagnosed in the previous studies? Although unlikely, the clinical impact of akathisia might have been underestimated. Another possibility is that akathisia was not categorized in the list of psychiatric diagnoses in the previous studies. Akathisia is not listed among the mental and behavioral disorders in the ICD-10 classification and DSM-III; DSM-IV newly adopted it as an axis I disorder. Another important factor is the misuse of prochlorperazine. Morphine was administered in 18 of 20 cases with akathisia in the present study. Nausea and vomiting is an initial adverse reaction in patients taking oral morphine. Prochlorperazine had been given to treat nausea induced by morphine, but its long-term administration was continued for no clear reason in almost all the cases.

Although psychotropic drugs are often used in palliative care, adverse drug reactions to psychotropics are sometimes overlooked. Two cancer patients who developed neuroleptic malignant syndrome, a potentially lethal adverse reaction of psychotropic drugs, have been reported previously. These patients developed neuroleptic malignant syndrome following bone marrow transplantation and in an intensive care unit on the day of surgery. The malignant syndrome was overlooked (Onose et al., 2002; Kawanishi et al., 2005). Diagnosing such adverse reactions is difficult due to multiple complicating factors associated with cancer treatment; its unfamiliarity to clinical oncologists, and occasionally the resemblance of these neuropsychiatric symptoms to those associated with cancer.

Akathisia is uncomfortable for patients; Atbaşgülu et al. (2001) found that the subjective awareness of akathisia is associated with suicidal ideation. Although akathisia is commonly observed in patients treated with neuroleptic drugs, it is sometimes overlooked or misdiagnosed (Weiden et al., 1987; Hirose, 2003). Akathisia often occurs without the coexistence of other extrapyramidal symptoms, and its characteristic symptoms, including inner restlessness,

tend to be regarded as representations of a symptom of a primary psychiatric illness. Therefore akathisia can be overlooked or misdiagnosed sometimes even in psychiatric units.

Based on these results, the use of antiemetic drugs should be optimized. In addition, clinical oncologists should be aware of akathisia. The management of adverse drug reactions is necessary during palliative care and contributes to patients' quality of life.

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CASE REPORT

Detection and treatment of akathisia in advanced cancer patients during adjuvant analgesic therapy with tricyclic antidepressants: Case reports and review of the literature

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ABSTRACT

Objective: There is substantial evidence that tricyclic antidepressants are effective in the management of chronic pain, including cancer pain. In oncological settings, these agents are used as adjuvant analgesic drugs. However, cases of akathisia due to tricyclic antidepressants used as adjuvant analgesic therapy have not previously been reported.

Case reports: Two cancer patients experiencing chronic pain who were refractory to nonsteroidal anti-inflammatory drugs and opioids were prescribed amoxapine as an adjuvant analgesic therapy for neuropathic pain. These patients developed inner restlessness and restless physical movements after amoxapine was prescribed. Although symptoms were atypical, akathisia was suspected and discontinuation of amoxapine resolved the symptoms.

Results and significance of results: Akathisia should be considered in patients receiving adjuvant analgesic therapy with tricyclic antidepressants. Early detection and appropriate treatment will relieve this distressing symptom. Restless movements involving parts of the body other than the legs may be the clue to the diagnosis.

KEYWORDS: Cancer, Pain control, Akathisia, Tricyclic antidepressants

INTRODUCTION

Akathisia is a common adverse effect of antipsychotics and, less commonly, antidepressants (Khawam et al., 2006). The clinical picture of akathisia involves subjective complaints of restlessness accompanied

by observable restless movements (e.g., fidgety movements of the legs, rocking from foot to foot, pacing, or the inability to sit or stand still) developing within a few weeks of starting or raising the dose of antipsychotics and/or antidepressants (American Psychiatric Association, 1994). The reported prevalence of akathisia has varied between 20% and 75%. Its onset is within a few days of initiation of medication, but it can also occur later in the treatment course (Hsin-Tung & Simpton, 2000).

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Akathisia can cause great discomfort and even agitation and is often described by the patient as the most distressing sensation, and suicide is a reported complication (Shear et al., 1983; Atbaşğlu et al., 2001). However, the condition is often underdiagnosed or misdiagnosed as anxiety, agitation, and violent behavior (Siris, 1985; Rodgers, 1992; Hirose, 2003). The reasons for underdiagnosis are considered related to both the patient's symptoms and the clinician's attitude toward akathisia. Patient-related factors include mild degree of akathisia, lack of apparent motor restlessness, lack of clear communication about subjective sensations of restlessness, restlessness in body areas other than the legs, and other clinical signs. Clinician-related factors include overemphasis on objective restlessness, failure to consider akathisia during antipsychotic therapy, and failure to fully implement antiakathisia treatments in ambiguous cases (Hirose, 2003).

There is substantial evidence that tricyclic antidepressants are effective in the management of chronic pain, including cancer pain (Botney & Fields, 1983; Hamon et al., 1987; Magni et al., 1987). In oncological settings, these agents are used as adjuvant analgesic drugs and are administered along with a primary analgesic, usually an opioid, to treat pain that is refractory to analgesic treatment alone (Portenoy, 2001). However, cases of akathisia due to tricyclic antidepressants used as adjuvant analgesic therapy have not previously been reported.

In this communication, we report two advanced cancer patients who developed akathisia due to adjuvant analgesic therapy with tricyclic antidepressants.

To standardize physicians' judgements, Francis' criteria (Francis et al., 1990) were proposed to diagnose akathisia. These criteria are based of a combination of clinical assessment and medical chart review, and the potential cause was categorized as (1) definite, if it was temporally related, there was laboratory confirmation, the patient improved with treatment or cessation of the offending agent, and there was no other cause present or (2) probable, if all the previous criteria were met but another main cause was present or laboratory confirmation was not achieved. In this study, we used the probable criteria because akathisia was confirmed only by clinical observation and careful inquiry, not by laboratory data.

CASE REPORTS

Case 1

A 39-year-old female had been diagnosed as having breast cancer 8 years previously and had received a

mastectomy followed by chemotherapy and hormonal therapy. Metastasis of cancer was recognized in the liver and bone and chemotherapy was performed. She developed lumbago that was refractory to non-steroidal anti-inflammatory drugs and opioids and was thought to be neuropathic in origin. She was administered 75 mg/day of amoxapine, an tricyclic antidepressant, as an adjuvant analgesic therapy. Five months after administration of amoxapine, she suddenly became restless and moved her arms and upper part of the body back and forth. She reported a sensation of inner restlessness in both upper arms, abdomen, and back, but denied such inner restlessness in the lower extremities or legs. Based on this clinical picture, akathisia was suspected, although clinical findings were atypical in that restlessness in the legs was not observed. Amoxapine was discontinued and the inner restlessness was resolved the next day.

The clinical findings and effective alleviation of symptoms after discontinuation of medication fulfilled Francis' criteria for drug-induced akathisia.

Medical history

The patient was a housewife, and had no medical history of psychiatric illness or alcohol or drug abuse. She had a normally cooperative character and was kind to others.

Case 2

A 54-year-old rectal cancer patient developed pain of the left lower thigh. He was treated with 180 mg of loxoprofene sodium, 1.8 mg of fentanyl, and 10 mg of prochlorperazine for about 1 month. As the pain was refractory to conventional therapy and thought to be neuropathic in origin, he was prescribed 10 mg of amoxapine as an adjuvant analgesic therapy. Ten days after administration of amoxapine, he sometimes woke up and walked around the ward slowly, but could not continue because of poor physical condition. He sometimes chewed gum and sucked candies. After careful inquiry, he reported a subjective sensation of inner restlessness in the lower extremities. As akathisia was suspected, prochlorperazine was discontinued first because of the dopamine receptor blockade property of prochlorperazine; however, symptoms of akathisia did not change during the following 2 days. Then amoxapine was discontinued and both motor and inner restlessness were resolved in 2 days. He also stopped chewing gum and sucking candies. The patient explained that he had felt restlessness in the mouth and chewed gum and sucked candies to relieve this sense of inner restlessness.

The clinical findings and effective alleviation of symptoms after discontinuation of medication fulfilled Francis' criteria for drug-induced akathisia.

Medical history

The patient had no medical history of psychiatric illness or alcohol or drug abuse. He had normally cooperative character and was kind to others.

DISCUSSION

Tricyclic antidepressants can be used as adjuvant analgesic drugs. Experimental studies indicate that these drugs potentiate the action of morphine by blocking serotonin reuptake and enhancing the action of serotonin at the spinal terminals of the opioid-mediated intrinsic analgesia system (Botney & Fields, 1983; Hamon et al., 1987).

These drugs also have extrapyramidal side effects, and amoxapine has been shown to have neuroleptic properties along with antidepressant effects (Krishnan et al., 1984; Apiquian et al., 2005). It appears that the 7-hydroxy metabolite of amoxapine causes a dopamine receptor blockade (Dolton, 1981).

We reported two cases of akathisia due to tricyclic antidepressants administered for adjuvant analgesic therapy. This is the first report of akathisia induced by adjuvant analgesic therapy using tricyclic antidepressants. Our report suggests that akathisia should be considered a possible side effect during adjuvant analgesic therapy.

In diagnosing akathisia, the typical clinical picture includes inner restlessness and fidgety and restless movement of the body, particularly in the legs. DSM-IV criteria describe restless movements expressed mainly in the legs, and these movements are considered highly characteristic to akathisia (American Psychiatric Association, 1994). However, it has been reported that restless movements may occur in other areas of the body such as arms or abdomen (Ratey & Salzman, 1984; Walters et al., 1989) and may present as dyspnea (Hirose, 2000). It has been reported that leg restlessness is recognized in only 27% (Gibb & Lees, 1986) and 55% (Sachdev & Kruk, 1994) of the cases.

Case 1 did not report inner restlessness or show restless movements involving the lower extremities or legs. In case 2, restlessness in the mouth has been reported and the patient relieved this sensation in the mouth by chewing gum. And it was difficult to recognize restless movements because the physical condition of the patient was poor and he lay down on the bed almost all day. Although the clinical pictures of akathisia in these patients included atypical

features, discontinuation of the suspected drug effectively alleviated symptoms.

Our study suggests that it is important to detect signs and symptoms of akathisia from these subtle combinations of movements. Slow but repeated movements and atypical movements involving areas other than legs together with reports of inner restlessness might be clues to diagnose these patients. The temporal relationships between administration of the drug and the development of symptoms are also important.

Physicians, nurses, pharmacists, and other health professionals should be aware of this possible side effect during adjuvant analgesic therapy. Early detection and appropriate management will improve the quality of life for these patients.

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