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

[a]Eight 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 ± *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; Atbaşğlu 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 coexistense 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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Palliative and Supportive Care (2007), 5, 411–414. Printed in the USA.
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DOI: 10.1017/S1478951507000612

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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(RECEIVED February 12, 2007; ACCEPTED March 2, 2007)

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 at 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 nonsteroidal 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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Eur J Clin Pharmacol (2007) 63:991–996
DOI 10.1007/s00228-007-0355-8

PHARMACOGENETICS

Effects of CYP2D6 polymorphisms on neuroleptic malignant syndrome

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Received: 5 May 2007 / Accepted: 23 July 2007 / Published online: 14 August 2007
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Abstract
Objective Neuroleptic malignant syndrome (NMS) is one of the most serious adverse reactions to antipsychotic medications. We accumulated data on Japanese NMS patients and, in a study designed to examine the effects of drug metabolism on the occurrence of NMS, tested the possibility of association between NMS and *CYP2D6* polymorphisms.
Methods We studied 53 patients who had experienced NMS and 112 healthy individuals. We determined what drugs the patients with NMS had been given and retrospectively identified candidates for drugs causing NMS. We screened the prevalence of *CYP2D6* genotypes using polymerase chain reaction and restriction fragment length polymorphism analyses.
Results The prevalence of **5* alleles in the group of all patients with NMS was higher than that in the controls, though this difference was not statistically significant (10.4% vs. 5.4%; P=0.107; odds ratio (OR) 2.05; 95% confidence interval (CI) 0.87–4.80). No association was found between the frequency of **10* alleles and the occurrence of NMS. We found **4* and duplicated alleles in only one patient each among the patients with NMS. A total of 29 patients appeared to have developed NMS as a result of having taking CYP2D6 substrates. The prevalence of **5* alleles in these 29 patient was significantly higher than that in the controls (15.5% vs. 5.4%; P=0.020; OR 3.25; 95% CI 1.30–8.13).
Conclusion Our findings suggest that the *CYP2D6*5* allele is likely to affect vulnerability to development of NMS.

Keywords Adverse reaction · CYP2D6 · Gene deletion · Neuroleptic malignant syndrome · Polymorphism

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Introduction

Neuroleptic malignant syndrome (NMS) is a well-recognized, severe, and potentially lethal adverse reaction to antipsychotic administration [1]. In addition to neuroleptic drugs, NMS can be caused by antidepressants, lithium carbonate, and other psychotropic agents. NMS is characterized by hyperthermia, extrapyramidal signs, altered consciousness, fluctuating blood pressure, incontinence, and dyspnea, as well as other features [2]. The frequency of its occurrence with conventional antipsychotic agents has been reported to vary from 0.02% to 2.44%, whereas a review of case reports has indicated that atypical antipsychotic agents can cause NMS, which can in some instances be severe enough to be fatal [3]. Caroff et al. and Ananth et al. reported the mortality rate is 4.4–11.3% [4, 5].

CYP2D6, an isozyme among the CYP mono-oxygenases, is responsible for the hepatic metabolism of various psychotropic agents. More than 40 polymorphic alleles that affect enzymatic activity have been described for the *CYP2D6* genes (http://www.imm.ki.se/cypalleles/cyp2d6.htm). The phenotypes of CYP2D6 activity resulting from these polymorphisms can be divided into extensive, poor,

and ultrarapid metabolizers (EM, PM, and UM) according to enzymatic activities [6]. The PM phenotype, lacking CYP2D6 expression, is caused by total gene deletion or single-nucleotide polymorphisms in a gene inherited in an autosomal recessive fashion. Together with the gene deletion allele (**5*), the polymorphic *CYP2D6* alleles **3* and **4* account for most instances of PM phenotype in Caucasians, although **3* and **4* are rare in Eastern Asians. Instead, the **10* allele, which encodes an unstable enzyme with decreased catalytic activity, is relatively frequent in Eastern Asia [7]. The frequency of the **5* allele is similar (4 to 6%) in Caucasian and East Asian populations [6]. Nishida et al. reported that the allelic frequencies of **10*, **5*, **4*, and **3* were 38.1%, 4.5%, 0.2%, and 0%, respectively, in 206 healthy Japanese subjects [8].

The PM phenotype is clinically important, as lack of the associated metabolic pathway may lead to toxicity and adverse reactions upon administration of certain drugs in standard doses [6, 9]. On the other hand, several studies have identified individuals with NMS who possessed *CYP2D6* polymorphisms resulting in defective CYP2D6 activity [10–12]. In this study, we performed systematic screening for *CYP2D6* polymorphisms and assessed genetic associations with the occurrence of NMS in Japanese patients.

Methods

We studied 53 patients (29 men and 24 women) who had experienced NMS. The patients had been recruited from several hospitals since 1996. NMS was diagnosed according to the criteria of Pope et al. [13]. Psychiatric diagnoses were made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*). Our control subjects were 112 healthy individuals without psychiatric diagnoses (33 men and 79 women). We recruited control subjects from personnel in hospitals and students, and we carried out the Mini-International Neuropsychiatric Interview (MINI) to exclude psychiatric patients. All subjects were Japanese and unrelated. We presented all NMS patients and healthy controls that we have accumulated so far. The prevalence of *CYP2D6*3*, **4*, and **10* in a part of our samples were previously reported elsewhere [7, 14].

We determined the drugs that the patients with NMS had been given and retrospectively identified candidates for drugs causing NMS. If NMS occurred after increase of an antipsychotic drug, we regarded the drug as a candidate. If sudden discontinuation of antipsychotics or antiparkinsonian drugs caused NMS, we mentioned it in the Table 1. In the other cases, we listed all psychotic drugs the patients were given.

This study was approved by the ethics committee of the Yokohama City University School of Medicine. Written informed consent was obtained from all of the patients and control subjects.

Genetic analysis

Genomic DNA was extracted from peripheral white blood cells from all patients and control subjects using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA) according to manufacturer guidelines. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analyses were performed to screen for **10* and **4* alleles according to the method of Wang et al. [15] and Kawanishi et al. [14]. Long PCR was performed to screen for *CYP2D6* gene deletion allele (*CYP2D6*5*) and duplicated alleles according to the method of Lundqvist et al. [16] for duplication and that of Johansson et al. [17] and Wennerholm et al. [18] for deletion using two sets of oligonucleotide primers in each PCR reaction. Alleles for which neither **10*, **5*, **4* nor duplicated alleles could be identified were classified as *CYP2D6*1* (wild-type) alleles. Genetic analyses were performed by an investigator unaware of which subjects had developed NMS.

Statistical analysis

Statistical analyses were performed using the χ^2 tests with Fisher's exact test. Statistical tests were two-tailed, with P values less than 0.05 considered significant. These analyses were performed using SPSS 11.0 for Windows (SPSS Japan, Tokyo).

Results

Table 1 shows characteristics of the patients with NMS. Mean age at the first NMS episode was 50.8 years [standard deviation (SD)=16.8). NMS relapsed in ten patients. The principal diagnoses were schizophrenia in 41 cases; mood disorders in four; delusional disorder, alcohol dependence, drug dependence, dementia, steroid-induced psychotic disorder, psychotic disorder due to viral encephalitis, autism, and personality disorder in one case each. CYP2D6 genotypes and allele frequencies of the NMS patients and control subjects are given in Table 2. The observed frequency of **5* alleles in patients with NMS was higher than that in controls, though the difference between groups was not statistically significant [10.4% vs. 5.4%; P=0.107; odds ratio (OR) 2.05; 95% confidence interval (CI) 0.87–4.80). No association was found between **10* alleles and the occurrence of NMS. The**4* and duplicated

Table 1 Characteristics of the patients with neuroleptic malignant syndrome (NMS)

Number	Sex (M/F)	Age of first NMS onset	Times of NMS	Diagnosis	Genotype	Possible causative drugs of NMS occurrence [1]
1	M	54	1	Schizophrenia	*1/*1	HPD
2	F	45	1	Schizophrenia	*1/*10	Bromperidol
3	M	46	1	Schizophrenia	*1/*10	Unknown
4	M	30	1	Schizophrenia	*1/*5	Fluphenazine
5	M	41	3	Schizophrenia	*10/*10	[a]Mosapramine, [b]HPD, [c]risperidone
6	F	72	2	Schizophrenia	*1/*10	[a]HPD, [b]sulpiride
7	M	40	1	Schizophrenia	*1/*1	Risperidone, thioridazine
8	M	59	2	Schizophrenia	*5/*10	[a]HPD, [b]HPD
9	M	76	1	Schizophrenia	*1/*5	Amoxapine, CPZ
10	M	43	2	Alcohol dependence	*1/*1	[a]Levomepromazine, [b]unknown
11	F	24	2	Schizophrenia	*1/*1	[a]Sulpiride, [b]CPZ, sultopride
12	M	28	1	Schizophrenia	*1/*1	HPD
13	F	60	1	Mood disorder	*1/*10	Amoxapine, amitriptyline
14	M	16	1	Schizophrenia	*10/*10	HPD
15	F	26	2	Schizophrenia	*1/*10	[a]HPD, propericyazine, [b]thioridazine
16	F	24	1	Schizophrenia	*1/*1	Bromperidol, discontinuation of biperiden
17	F	20	1	Schizophrenia	*1/*1	Risperidone
18	M	55	4	Psychotic disorder due to viral encephalitis	*1/*1	[a]Li , [b]unknown, [c]Li, HPD, [d]levomepromazine
19	M	30	1	Schizophrenia	*1/*10	Nemonapride
20	F	62	2	Schizophrenia	*4/*10	[a]Bromperidol, [b]Discontinuation of neuroleptics
21	M	57	1	Mood disorder	*1/*1	Amitriptyline, levomepromazine
22	F	74	1	Schizophrenia	*1/*10	HPD
23	M	48	1	Mood disorder	*1/*1	Mianserin
24	F	31	1	Schizophrenia	*5/*10	Risperidone, olanzapine
25	F	32	1	Schizophrenia	*10/*10	HPD
26	M	21	1	Schizophrenia	*10/*10	HPD
27	F	62	1	Schizophrenia	*1/*1	Discontinuation of HPD and bromperidol
28	F	38	1	Personality disorder	*1/*1	Sultopride
29	M	30	1	Drug dependence	*1/*1	Mianserin, levomepromazine
30	F	51	1	Schizophrenia	*1/*10	Risperidone, perospirone
31	F	31	1	Schizophrenia	*1/*5	Levomepromazine, propericyazine, perospirone
32	M	34	1	Schizophrenia	*10/*10	HPD
33	M	73	1	Schizophrenia	*10/*10	Risperidone, tiapride
34	M	19	1	Schizophrenia	*1XN/*1	Quetiapine
35	F	38	1	Schizophrenia	*1/*1	HPD, CPZ
36	M	21	1	Schizophrenia	*1/*1	Zotepine, bromperidol
37	F	65	1	Schizophrenia	*1/*1	Risperidone, nemonapride, CPZ
38	M	9	1	Autism	*1/*5	HPD
39	M	66	1	Dementia	*1/*5	Quetiapine
40	F	68	1	Mood disorder	*1/*1	Reduced amantadine
41	F	54	2	Schizophrenia	*1/*5	[a]HPD, CPZ, levomepromazine, sulpiride, tiapride, [b]CPZ
42	F	58	2	Steroid-induced psychotic disorder	*10/*10	[a]Perospirone [b]reduced bromocriptine
43	M	47	1	Schizophrenia	*1/*1	HPD
44	M	21	1	Schizophrenia	*1/*10	Sultopride
45	M	34	1	Schizophrenia	*1/*1	Sultopride, zotepine
46	M	49	1	Schizophrenia	*1/*5	Risperidone, quetiapine
47	M	26	1	Schizophrenia	*10/*10	Discontinuation of antipsychotics
48	M	66	1	Schizophrenia	*1/*1	Risperidone, zotepine

Table 1 (continued)

Number	Sex (M/F)	Age of first NMS onset	Times of NMS	Diagnosis	Genotype	Possible causative drugs of NMS occurrence [1]
49	M	58	1	Schizophrenia	*5/*10	HPD
50	F	71	1	Schizophrenia	*1/*10	Levomepromazine
51	F	56	1	Delusional disorder	*10/*10	Quetiapine
52	F	35	1	Schizophrenia	*1/*5	Risperidone, levomepromazine
53	F	71	1	Schizophrenia	*1/*10	Zotepine

[1] *HPD* haloperidol, *CPZ* chlorpromazine, *Li* lithium carbonate
[a], [b], [c], and [d] indicate the first, second, third, and fourth episodes of NMS, respectively.

alleles were found in only one patient each among the NMS group.

To estimate the clinical effects of deletion, NMS patients were classified into those whose NMS-causative drugs had been CYP2D6 substrates. A total of 29 patients had been given CYP2D6 substrates (risperidone, olanzapine, fluphenazine, thioridazine, haloperidol, chlorpromazine, amitriptyline, or mianserin [9]) (Table 1). The prevalence of **5* alleles in these 29 patients was significantly higher than that in controls (15.5% vs. 5.4%; P=0.020; OR 3.25; 95% CI 1.30–8.13).

Discussion

Since NMS was first proposed as a clinical entity in the 1960s, various case descriptions and clinical studies of it have been reported from psychiatric and neurologic units, though the mechanisms underlying NMS remain unclear. Dopaminergic systems of the central nervous system appear likely to be involved in the onset of NMS, as all neuroleptics known to cause NMS act as dopamine receptor antagonists [1]. Certain predisposing conditions such as dehydration, malnutrition, exhaustion, infection, and organic brain diseases are risk factors for the development of NMS [19–23]. High or rapidly increasing antipsychotic doses, large numbers of intramuscular injections, and psychomotor agitation are additional risk factors that tend to be interrelated [19, 20]. On the other hand, NMS often recurs despite absence of acquired risk factors. In addition, occurrences of familial NMS have been reported. Deuschl et al. reported NMS in twin brothers with schizophrenia [24], and Otani et al. described familial occurrence involving a mother and her two daughters [25]. Furthermore, patients who have experienced NMS remain at increased risk for its occurrence [1, 26–29]. These findings suggest that constitutional factors under genetic control play roles in the onset of NMS, which has spurred mutation analyses and genetic association studies. Although minimization of risk factors and increased awareness of NMS could decrease its incidence, and detection of prodromal symptoms could decrease the morbidity of NMS, prediction and prevention are still difficult, as there are individual differences in responses to drugs, and no biological marker is available to identify individuals who are inherently at increased risk for NMS.

Table 2 CYP2D6 genotypes and allele frequencies in patients with neuroleptic malignant syndrome (NMS) and control patients (%)

	Controls (n=112)	Patients with NMS (n=53)	Patients with NMS caused by drugs including CYP2D6 substrates (n=29)
Genotypes			
*1/*1	46 (41.1)	20 (37.7)	11 (37.9)
*1/*10	32 (28.6)	11 (20.8)	4 (13.8)
*10/*10	21 (18.8)	9 (17.0)	5 (17.2)
*1/*5	8 (7.1)	8 (15.1)	6 (20.7)
*5/*10	4 (3.6)	3 (5.7)	3 (10.3)
*4/*10	0	1 (1.9)	0
*1XN/*1	1 (0.9)	1 (1.9)	0
Alleles			
*1	133/224 (59.4)	60/106 (56.6)	32/58 (55.2)
*10	78/224 (34.8)	33/106 (31.1)	17/58 (29.3)
*5	12/224 (5.4)	11/106 (10.4)	9/58 (15.5)[a]
*4	0	1/106 (0.9)	0
*1XN	1/224 (0.4)	1/106 (0.9)	0

[a] $\chi 2$, Fisher's exact test, $p<0.05$

Recent findings of pharmacogenetic studies have indicated that polymorphisms of the *CYP2D6* gene are associated with interindividual differences in drug responses. PM individuals who are homozygous for either point mutations in or deletion of the *CYP2D6* gene are unable to metabolize CYP2D6 substrates, resulting in higher plasma drug concentrations. The PM phenotype is clinically important, as lack of the associated metabolic pathway may lead to toxicity and adverse reactions upon administration of drugs in standard doses [6, 9]. Dose effect of the *CYP2D6* gene has been shown to be associated with CYP2D6 activity, and this activity is decreased in individ-

uals heterozygous for deletion [6]. Several studies have suggested that adverse reactions to neuroleptics are associated with decreased or deficient CYP2D6 activity. PM is more prevalent among patients with than those without drug-induced extrapyramidal symptoms [30, 31]. For example, tardive dyskinesia (TD) has been linked to decreased CYP2D6 activity. Kapitany et al. genotyped patients with schizophrenia for the **3*, **4*, and **5* alleles and found that frequency of TD was higher in patients heterozygous for these alleles [32]. Ohmori et al. also found an association between TD and the **10* allele in Japanese patients with schizophrenia [33]. Similar conclusions were obtained in another study [30, 34].

Genetic association studies also have sought to identify *CYP2D6* polymorphisms affecting susceptibility to NMS. We also reported the finding of homozygosity for the *CYP2D6*10* allele in two psychiatric patients who had previous episodes of NMS, although we failed to identify an association between the **3*, **4*, or **10* allele and NMS in previous studies [7, 11, 14]. Recently, we reported two NMS patients with schizophrenia who were found to possess a *CYP2D6* gene-deletion allele [12].

Thus, in the study reported here, we reexamined the possibility of an association between CYP2D6 polymorphisms including the **5* allele and NMS in 53 patients with NMS. We found that the prevalence of **5* alleles in the 29 patients whose NMS-causative drugs were CYP2D6 substrates was significantly higher than that in controls (15.5% vs. 5.4%; P=0.020), though we did not find a significant difference in prevalence of **5* alleles between the group of patients with NMS and controls (10.4% vs. 5.4%; P=0.107).

On the other hand, no association was found between NMS and **10* or **10/*10* genotypes. The frequency of genotype of either **5/*10*, **4/*10*, **10/*10*, or **1/*5* tended to be higher in NMS patients whose NMS-causative drugs were CYP2D6 substrates than that in controls (P= 0.076). Kubota et al. found that no difference was observed in metabolic activity of dextromethorphan O-demethylation between individuals with **10/*10* and **1/*5* genotypes [35]. Mihara et al. reported that the steady-state plasma concentrations of equal doses of risperidone were not significantly different between **10/*10* and **5/wt* [36]. Another study investigating haloperidol metabolism indicated that **5* might have stronger impact than **10* [37]. The two polymorphic alleles, **10* and **5*, possibly have different impacts in drug metabolism.

CYP2D6 substrates taken by patients with a **5* allele were metabolized at a reduced rate, resulting in higher plasma levels of the CYP2D6 substrate; it is the same condition as that brought on by known risk factors of NMS: rapidly increasing or greater numbers of intramuscular injections of neuroleptic drugs. We speculate that accumulation or high plasma concentrations of CYP2D6 substrates may have induced cellular toxicity and/or aberrant neurotransmission linked to the pathogenesis of NMS. Screening for at least the *CYP2D6*5* allele before initiating antipsychotic therapy including CYP2D6 substrates might be useful in identifying subjects at risk of developing NMS.

The following limitations to our study should be noted: we did not know whether sulpiride, sultopride, levomepromazine, propericyazine, and mosapramine are CYP2D6 substrates; we did not consider causes of NMS other than medications because physical conditions of the patients were not fully investigated in this study; and we lacked laboratory data concerning serum concentrations of antipsychotics because this study was retrospective and we could measure only a few serum concentrations of antipsychotics, given the constraints of the Japanese health insurance system.

NMS may be a heterogeneous condition with respect to etiology. We believe that by themselves, *CYP2D6* gene polymorphisms such as the **5* allele cannot explain all occurrences of NMS. Systemic analyses involving functional genetic polymorphisms of drug targets, such as dopamine receptors [38], may also be needed to improve understanding of this disorder. Our findings do suggest, though, that the *CYP2D6*5* allele is likely to affect vulnerability to development of NMS. Although 53 patients is a small number for an association study, NMS occurs only rarely, and this number is the greatest in a genetic study of NMS to date. Whereas our sample size has been the greatest for an association study regarding NMS to date, it is still small. Larger case-control studies will be needed to assess the effects of *CYP2D6* gene polymorphisms on the occurrence of NMS.

Acknowledgements This study was supported in part by a Grant-in-Aid for Scientific Research (No. 16790698) from the Ministry of Education, Science, Sports, and Culture, Japan.

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Palliative and Supportive Care (2008), 6, 79–81. Printed in the USA.
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DOI: 10.1017/S1478951508000114

CASE REPORT

A case of respiratory akathisia in a cancer patient: A case report

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(RECEIVED September 14, 2007; ACCEPTED October 16, 2007)

ABSTRACT

Objective: It has been reported that akathisia is a neurological side effect induced by antiemetic drugs and/or antipsychotics. Akathisia can occur in any area of the body, but respiratory akathisia is an unusual type of akathisia. Cases of respiratory akathisia in cancer patients taking antiemetic drugs have not previously been reported.

Methods: We report on a case of a cancer patient taking prochlorperazine as an antiemetic drug who experienced dyspnea accompanied by severe restlessness associated with respiration. By administration of biperiden, his restlessness in respiration and dyspnea promptly disappeared.

Results: This finding led us to conclude that this cancer patient was experiencing respiratory akathisia.

Significance of results: Respiratory akathisia is uncommon. It is important for cancer patients that dyspnea induced by disease progression be ruled out as a cause of the respiratory restlessness. It is necessary to consider the possibility of akathisia in patients that complain of vague anxiety, chest discomfort, or dyspnea following antipsychotic medication.

KEYWORDS: Respiratory akathisia, Cancer, Antiemetic drug

INTRODUCTION

Akathisia is a neurological side effect produced by antipsychotic or antiemetic drug therapy (Blaisdell, 1994). The clinical picture of akathisia is a feeling of inner restlessness in the limbs, especially in the legs (Gibb & Lee, 1986). However, reports have indicated that akathisia can occur in any area of the body, such as the arms or abdomen (Raskin, 1972; Ratey & Salzman, 1984; Walters et al., 1989). A rare manifestation of akathisia reported by patients receiving antipsychotic treatment is an inner restlessness in respiration as dyspnea.

Prochlorperazine is an antiemetic agent frequently used by cancer patients taking opioids (e.g., morphine, oxycodone) for cancer pain. In oncological settings, prochlorperazine is used as an antiemetic drug for nausea, a side effect of opioid. It is a phenothiazine antiemetic that has central dopamine antagonist properties and that has been reported to cause acute extrapyramidal side effects,

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parkinsonism, dystonia, and akathisia (Bateman et al., 1989). It is well known that neuroleptic-induced akathisia may be difficult to recognize and can occur in the absence of other extrapyramidal signs. Furthermore, cases of akathisia due to antiemetic drugs used by cancer patients have been little reported.

CASE REPORT

The patient was an 66-year-old man with squamous cell carcinoma of the esophagus, stage II(T2N0M0). Due to his renal impairment and the presence of emphysema, surgical resection was not performed; furthermore, chemotherapy was not indicated. Therefore, he attempted radiation therapy and received a total dose of 70.2 Gy. He used opioid, 20 mg/day of morphine hydrochloride, for pain of esophagitis by irradiation, with taking prochlorperazine as an antiemetic drug. He complained of chest discomfort after receiving 5 mg/day of prochlorperazine p.o. for 3 weeks and was admitted to the hospital. When he arrived in the hospital, he acknowledged dyspnea with vague anxiety and a subjective restlessness in respiration, with a temperature of 36.8°C, blood pressure of 118/72 mm Hg, pulse 79 beats/min, respiratory rate 18 breaths/min. Resting room-air oxygen saturation was 98%. First, radiation pneumonitis was suspected, but chest X-ray was normal. He felt that he could not respire leisurely nor stop breathing at any time because of this restlessness in respiration. He denied restlessness in the limbs or other body areas except for the chest. He showed no signs or symptoms of parkinsonism. He was administered 5 mg of biperiden d.i.v.; his restlessness in respiration and dyspnea simultaneously disappeared approximately 1 h later (Hirose & Ashby, 2000). Subsequently, 6 mg of oral biperiden was added to the treatment regimen. The next day, the dyspnea with vague anxiety and other restless movements completely ceased. No signs or symptoms of akathisia have appeared in this patient since that time.

DISCUSSION

We reported respiratory akathisia in cancer patients taking prochlorperazine as antiemetics. This is the first report of respiratory akathisia recognized in cancer patients.

It was necessary that other medical problems known to produce dyspnea, such as panic attacks and dyskinesia and dystonia or pulmonary diseases, could be ruled out as a cause of the respiratory restlessness (Hirose, 2000). In this case, the patient did not have anxiety about dying or a history of panic disorder before. Respiratory dyskinesia presents as involuntary movements of respiratory muscles, but not as a restless feeling in respiration, and is not improved on treatment with biperiden (Kruk et al., 1995; Esmail et al, 1999; Heard et al., 1999). Furthermore, in this case, dystonia was ruled out by the absence of tonic contractions of respiratory muscles (Dressler & Benecke, 2005).

Respiratory akathisia is uncommon, so one needs to ask specific questions about restlessness in breathing to recognize this type of akathisia. Therefore, if physicians is not aware of inner restlessness in respiration, it is possible that dyspnea in akathisia may be overlooked or misdiagnosed as a symptom of anxiety disorders, agitation, or respiratory symptoms of cancer itself (Hirose, 2000).

Antiemetics possessing a central antidopaminergic effect are suspected to have caused the akathisia (Seeman, 2002; Matsui-Sakata et al., 2005). Antiemetic-induced akathisia has been reported in cancer patients receiving metoclopramide or prochlorperazine to help control chemotherapy-related nausea and vomiting (Fleishman et al., 1994; Tsuji et al., 2006). In this case, prochlorperazine was used as an antiemetic drug for nausea and vomiting, a side effect of opioid.

Prochlorperazine is a phenothiazine antiemetic that has central dopamine antagonistic properties. It has been reported that the presumed community standard of prescribing prochlorperazine, dexamethasone, or a 5HT3 receptor antagonist after moderately high to highly emetogenic chemotherapy results in equivalent outcomes in terms of control of vomiting and measures of satisfaction and quality of life (Burris et al., 1996; Crucitt et al., 1996).

In Japan, many cancer patients taking opioids for cancer pain clinically use prochlorperazine as an antiemetic drug. Therefore, it should be noted that akathisia is considered a possible side effect during the management of cancer pain.

The clinicians' attitude toward akathisia is important to recognize. It is also important to consider the possibility of akathisia in patients that complain of vague anxiety, chest discomfort, or dyspnea following antipsychotic medication.

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original article

Annals of Oncology 19: 49–55, 2008
doi:10.1093/annonc/mdm494
Published online 26 October 2007

Psychological and behavioral mechanisms influencing the use of complementary and alternative medicine (CAM) in cancer patients

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Received 8 May 2007; revised 6 September 2007; accepted 14 September 2007

Background: This study explored the psychological and behavioral mechanisms of complementary and alternative medicine (CAM) use in Japanese cancer patients using two applied behavioral models, the transtheoretical model (TTM), and theory of planned behavior (TPB).

Patients and methods: Questionnaires were distributed to 1100 patients at three cancer treatment facilities in Japan and data on 521 cancer patients were used in the final analysis. The questionnaire included items based on TTM and TPB variables, as well as three psychological batteries.

Results: According to the TTM, 88 patients (17%) were in precontemplation, 226 (43%) in contemplation, 33 (6%) in preparation, 71 (14%) in action, and 103 (20%) in maintenance. The model derived from structural equation modeling revealed that the stage of CAM use was significantly affected by the pros, cons, expectation from family, norms of medical staff, use of chemotherapy, period from diagnosis, and place of treatment. The primary factor for the stage of CAM use was the expectation from family.

Conclusions: The findings revealed the existence of a number of psychologically induced potential CAM users, and psychological variables including positive attitude for CAM use and perceived family expectation greatly influence CAM use in cancer patients.

Key words: CAM, cancer patients, psychological adjustment, theory of planned behavior, transtheoretical model

introduction

Cancer patients use nutritional supplements, psychological techniques, and natural medical approaches together with conventional medicine, or in replace of conventional therapy, which are so-called complementary and alternative medicine (CAM). Recent surveys have demonstrated the high prevalence of CAM use by cancer patients. Sixty-seven percent of Canadian respondents reported using CAM, most often in an attempt to boost the immune system [1]. The first national survey on the use of CAM in Japan revealed that 45% of Japanese cancer patients have used CAM [2].

CAM is defined by the National Center for Complementary and Alternative Medicine as 'a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine' [3] In addition, a new operational definition of CAM was proposed that it should include patients' perspectives, such as individual goals, objectives, and beliefs of the patients [4]. Therefore, it is important to consider psychological aspects such as patients' background, reasons or intentions for using CAM in oncology.

Several studies have explored the background and reasoning behind CAM use [1, 5–7]. CAM use in early-stage breast cancer patients was regarded as a marker of greater psychosocial distress and a worse quality of life [7] and advanced-stage cancer patients who used CAM had higher levels of anxiety and pain, lower satisfaction with conventional medicine, and a lower need for control over treatment decisions [8]. Alternatively, the use of CAM by cancer patients has not been associated with perceived distress or poor compliance with medical treatment [9]. However, the psychological and behavioral mechanisms of CAM use have not yet been clarified. Therefore, we carried out a multicenter cross-sectional survey to explore the psychological mechanism of CAM use in Japanese cancer patients from patients' perspectives, using the transtheoretical model (TTM), and the theory of planned behavior (TPB).

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The TTM [10] is useful for explaining changes in health behavior and has been used in various programs such as smoking cessation [11], genetic testing for colorectal cancer [12], and mammography adoption [13]. In the TTM, the decisional balance between pros and cons—positive and negative attitudes for the behavior—will account for the state of change observed during five stages: precontemplation, contemplation, preparation, action, and maintenance [10]. We adopted this classification to explain the behavioral intention of patients using CAM in cancer treatment. Moreover, self-efficacy, which acts as a mediating function for the psychological adjustment of cancer patients [14, 15], is an important factor affecting a person's movement from one stage to another.

The TPB [16] examines behavioral intentions based on three major components: the patient's attitude towards the behavior, perceived control, and subjective norms. In cases of cancer patients, attitude towards behavior may include perceived effectiveness of treatment, anxiety regarding side-effects, etc. Perceived control is the individual's perception of the extent to which performance of the behavior is easy or difficult, and is synonymous with the concept of self-efficacy [16]. Subjective norms in cancer CAM include expectation from family members, and norms of medical staff towards the patients.

Our hypotheses are as follows: (i) cancer patients are classified into five stages of CAM use, (ii) the stage of CAM use is explained by TTM and TPB variables, and (iii) perceived control positively correlates with CAM use and mediates between CAM use and psychological adjustment.

patients and methods

participants

This study was approved by the institutional review boards of the Kinki Chuo Chest Disease Center, National Kyushu Cancer Center, and National Shikoku Cancer Center. From April 2005 to August 2005, a total of 1100 questionnaires were distributed to patients at each institute. Patients were enrolled in the study after their attending physician assessed if they met the following conditions: were receiving medical treatment through the outpatient or inpatient units at any of the three cancer centers, had an Eastern Cooperative Oncology Group performance status [17] from zero to three, were physically able to fill in the questionnaires by themselves, and had no cognitive impairment. On the questionnaire, we explained the purpose of the study and the fact that returning the questionnaire would be regarded as consent for participation; though we asked the patients to return the questionnaires anonymously.

measures

For this study, we developed our own questionnaire to examine CAM use in cancer patients (available from the authors). The questionnaire contained 85 items and it took about 20 min to complete. On the cover page of the questionnaire, CAM was defined using same definition of our previous survey [2]: 'as any therapy is not included in the orthodox biomedical framework of care for patients, which includes remedies used without the approval of the relevant government authorities of new drugs after peer review of preclinical experiments and clinical trials regulated by law. Health insurance does not usually cover the cost of CAM, and patients are generally liable for all expenses incurred by CAM use. CAM may include use of natural products from mushrooms, herbs, green tea, shark cartilage, megavitamins, or other special foods, and may incorporate acupuncture, aromatherapy, massage, meditation, etc'. Additionally, a sheet containing 20 examples of CAM therapies and products was attached to the questionnaire. The first portion of the questionnaire asked for information on the patients' background, including type of disease, age at onset, current age, gender, educational level, economic status, type of cancer treatment, satisfaction with treatment, smoking, drinking, and social support measured by the single item Tangible Social Support Scale [18].

The second part of the questionnaire included items originally designed to evaluate the cancer CAM-specific TTM and TPB variables. To measure the patients' subjective intention with regard to CAM use, we additionally defined cancer CAM use as those 'using any supplements or dietary foods or receiving any therapy that appears to have anticancer effects or auxiliary effect to that of conventional cancer therapy'. Respondents were asked to rate themselves based on the five stages of the TTM [10]: precontemplation ("I have no interest in using CAM"), contemplation ("I have been thinking that I might want to use CAM"), preparation ("I am preparing to use CAM"), action ("I have already used CAM in the last 6 months"), and maintenance ("I have already used CAM for >6 months"). The next section was composed of 27 items measuring TTM and TPB variables. The items were measured on a five-point Likert-type scale that ranged from 'not at all' (1) to 'extremely' (5). They included following five categories, (i) positive attitudes for CAM; (ii) pros; (iii) cons; (iv) expectation from family; and (v) norms of medical staff. The items were developed in our previous study on CAM [2] and another study on dietary food intake [19]. We used 16 from 27 items using confirmatory factor analysis on the current data as structurally valid and reliable items (Table 1). Also, content validity of the all TTM and TPB items in this part was confirmed by experts of two physicians, one psychiatrist and two psychologists.

To assess psychological adjustment, we used the Japanese version [20] of the Hospital Anxiety and Depression Scale (HADS) [21], which has 14 questions on anxiety and depression with each question rated from 0 to 3. The validity and reliability of the Japanese HADS in cancer patients has been confirmed previously [22].

To assess perceived control in patients, we used the Self-Efficacy for Advanced Cancer (SEAC) scale, which was designed to evaluate self-efficacy of cancer patients [23]. The SEAC scale has 18 items with three subscales: symptom coping efficacy, activities of daily living efficacy (ADE), and affect regulation efficacy (ARE). The scale was formatted on an 11-point Likert-type scale ranging from 0 (not at all confident) to 100 (totally confident). The reliability and validity of this scale were also confirmed [23].

Finally, the Japanese version of the MD Anderson Symptom Inventory (MDASI-J) [24] was developed as a brief multiple-symptom assessment scale. It consisted of 13 symptom items [25], and its validity and reliability were confirmed [24]. We used 10 of the 13 physical symptom items for our statistical analyses since the items for distress, sadness, and remembrance were significantly and highly correlated with the HADS total score ($r = 0.0479$, $P < 0.001$; $r = 0.456$, $P < 0.001$; $r = 0.334$, $P < 0.001$, respectively).

statistical analyses

Descriptive analyses were carried out summarizing the participants' backgrounds and scores following psychological measurements. Those with >30% missing values on the questionnaire were excluded from the analyses. The factors predicting stage of CAM use were analyzed through univariate analysis using the analysis of variance. In order to carry out multivariate analyses, we transformed the participants' responses for the stage of CAM use into a numeric scale ranging from 1 to 5 points (1, precontemplation; 2, contemplation; 3, preparation; 4, action; and 5, maintenance), according to a previous study [15]. Next, structural equation modeling (SEM) using the maximum likelihood method was carried out to

Table 1. Items measuring TTM and TPB variables and factor definitions

Items	Factor loadings
Positive attitudes for CAM (Cronbach alpha = 0.83)	
Definition: The items represented the high-perceived availability and importance of CAM use for the patients.	
1. CAM is important to retain physical strength.	0.80
2. Hospital care alone is not enough.	0.68
3. Convenience is an important determinant of starting to use CAM.	0.84
4. The cost of CAM is important.	0.66
Pros (Cronbach alpha = 0.90)	
Definition: The items represeinted patients' perceived positive outcomes of CAM use.	
5. The use of CAM leads to the cure of disease.	0.90
6. The use of CAM halts the progression of disease.	0.89
7. The use of CAM boosts physical and immune strength.	0.90
8. CAM has fewer side-effects compared with medical care.	0.69
Cons (Cronbach alpha = 0.70)	
Definition: The items represented patients' perceived negative outcomes of CAM use.	
9. The use of CAM has bad influence on medical care.	0.79
10. The use of CAM deteriorates disease.	0.89
11. I am aware of the side-effects of CAM.	0.53
12. I am aware of the dependence liability of CAM.	0.53
Expectation from family (Cronbach alpha = 0.65)	
Definition: The items represented patients' perceived expectations and recommendations from family.	
13. My family/friends believe that I should be actively engaged in the use of CAM.	0.74
14. My use of CAM is influenced by the opinions of my family/friends.	0.65
Norms of medical staff (Cronbach alpha = 0.34)	
Definition: The items represented patients' perceived expectation, recommendation from patients' medical staff, or their norms.	
15. My doctors/nurses believe that I should be actively engaged in the use of CAM.	0.68
16. My use of CAM is influenced by the opinions of my doctors/nurses.	0.30

Fit indices from the confirmatory factor analysis for items and factors indicated above: chi-square (96) = 345.5; $P = 0.001$; GFI = 0.92; AGFI = 0.88; CFI = 0.94; RMSEA = 0.07.
TTM, transtheoretical model; TPB, theory of planned behaviour; CAM, complementary and alternative medicine.

test the model. Because the model needed a parsimonious structure, we used the mean scores of SEAC as 'self-efficacy', the total score of HADS as 'psychological distress', and the mean scores of 10 items of MDASI-J as 'physical sympotom'. We conducted all statistical analyses using SPSS (version 14.0) and AMOS (version 5.0.1) software packages.

results

response rate to questionnaire

Of the 1100 questionnaires, 750 were given to inpatients and 350 to outpatients. Out of the 651 questionnaires returned (response rate 59.2%), 521 were valid for statistical analyses. The rest ($n = 130$) were invalid because of the lack of major information such as disease name or stage of CAM use. Moreover, questionnaires from noncancer patients were excluded from the analyses. Thus, the rate of valid replies was 47.4%.

backgrounds of patients and distribution of CAM use

The participants consisted of 246 males and 270 females, and five unknowns. Table 2 summarizes the demographic and diagnostic information of the participants. For staging, 88 patients (16.9%) were in precontemplation, 226 (43.4%) in contemplation, and 31 (6.6%) in preparation among the 347 CAM nonusers (66.6%), with 71 (13.6%) in action and 103 (19.8%) in maintenance among the 174 CAM users (33.4%). Table 1 also shows the prevalence of the five stages of CAM use categorized by demographic and medical status variables. The prevalence of CAM use in the higher stages, including action and maintenance, was significantly higher in patients who received chemotherapy ($P < 0.001$), those dissatisfied with current conventional treatment ($P < 0.05$), and outpatients ($P < 0.001$).

psychosocial factors associated with the stages of CAM use

Table 3 shows the mean response and the results of the univariate analyses for psychological variables, physical symptom variables, and social support obtained from patients at each of the five stages of CAM use. There were significant differences amongst patients in the five stages based on pros ($P < 0.001$), cons ($P < 0.001$), positive attitude for CAM ($P < 0.001$), and expectation from family members ($P < 0.001$). There was a slightly higher response on ADE ($P < 0.10$) in patients who were in the action and maintenance stages.

structural model for stages of CAM use

We carried out SEM by first selecting 14 variables in the initial model because they were observed to be significant predictors in the univariate analysis or were essential components for the TTM and TPB theories: use of chemotherapy, period from diagnosis, whether need for treatment was met, treatment place, stage of CAM use, psychological distress, pros, cons, positive attitude, expectation from family members, norms of medical staff, self-efficacy, psychological distress, physical symptoms, and social support. Next, we drew all paths according to the results of the correlation analysis. Since there was a significantly strong correlation between the pros and a positive attitude ($r = 0.80$, $P < 0.001$), and since the explanation by the TTM is given a priority for our purposes, we dropped positive attitude from the initial model. We repeated the SEM and sequentially dropped paths that were not significant until all the paths in the model became significant ($P < 0.05$). The variable 'met need for treatment' was dropped from the model because all the paths from this variable became not significant.

Figure 1 represents the final model. The fit indices for this model were excellent and included the following: chi-square

doi:10.1093/annonc/mdm494

Table 2. Patients' background and CAM use stage

	Total	Precontemplation		Contemplation		Preparation		Action		Maintenance		P (χ^2 test)
	n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Total	521	88	16.9	226	43.4	33	6.3	71	13.6	103	19.8	
Age years												
>60	262	47	17.9	120	45.8	13	5.0	31	11.8	51	19.5	0.446
≤60	253	40	15.8	105	41.5	19	7.5	40	15.8	49	19.4	
Gender												
Male	270	43	15.9	112	41.5	22	8.1	35	13.0	58	21.5	0.336
Female	246	45	18.3	110	44.7	11	4.5	36	14.6	44	17.9	
Education												
High school	318	50	15.7	141	44.3	7.2	7.2	46	14.5	58	18.2	0.561
Posthigh school	174	34	19.5	67	38.5	10	5.7	25	14.4	38	18.2	
Period from diagnosis												
≤1 year	261	56	21.5	118	45.2	20	7.7	46	17.6	21	8.0	0.000
>1 year	246	29	11.8	102	41.5	10	4.1	25	10.2	80	32.5	
Conventional treatment												
Chemotherapy	393	58	14.8	158	40.2	28	7.1	61	15.5	88	22.4	0.001
Nonchemotherapy	122	27	22.1	66	54.1	5	4.1	10	8.2	14	11.5	
Treatment met patient's needs												
Yes	371	72	19.4	161	43.4	18	4.9	49	13.2	71	19.1	0.045
No	150	16	10.7	65	43.3	15	10.0	22	14.7	32	21.3	
House income												
≥¥7 000 000	113	17	15.0	48	42.5	5	4.4	13	11.5	30	26.5	0.438
<¥7 000 000	334	53	15.9	144	43.1	23	6.9	50	15.0	64	19.2	
Treatment place												
Inpatient ward	360	67	18.6	167	46.4	27	7.5	53	14.7	46	12.8	0.000
Palliative care unit	24	2	8.3	8	33.3	5	20.8	3	12.5	6	25.0	
Outpatient clinic	161	21	13.0	59	36.6	6	3.7	18	11.2	57	35.4	
Cancer												
Lung	190	28	14.7	69	36.3	11	5.8	34	17.9	48	25.3	0.137
Breast	55	11	20.0	30	54.5	4	7.3	4	7.3	6	10.9	
Gastrointestinal	79	13	16.5	40	50.6	6	7.6	10	12.7	10	12.7	
Gynecological	61	8	13.1	28	45.9	2	3.3	7	11.5	16	26.2	
Other	121	24	19.8	54	44.6	9	7.4	13	10.7	21	17.4	

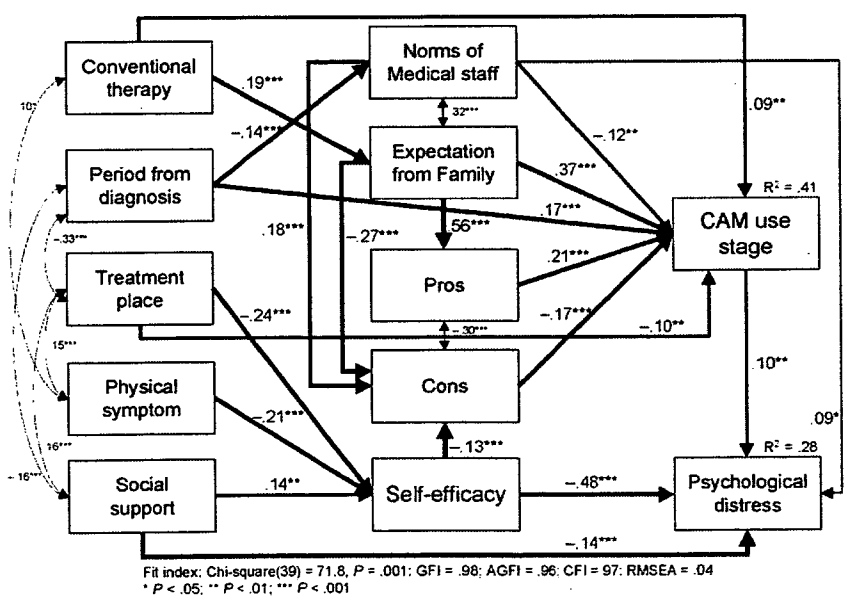

Figure 1. Structural model for the stage of CAM use and psychological adjustment.