interpretation we consider unlikely, because additional analysis of laboratory findings suggested that the blood urea nitrogen/creatinine level, a biological marker of dehydration, increased in the hydration group similar to the non-hydration group. The second interpretation seems also less likely, because a well-conducted open trial and a small randomized controlled trial indicated that artificial hydration therapy had limited beneficial effects in alleviation of thirst sensation for most terminally ill cancer patients [7, 9], and this study suggests that more active hydration would cause more fluid retention symptoms, limiting the use of hydration. On the other hand, the third interpretation is supported by an exploratory study indicating that the main pathophysiology of terminal dehydration is decreased intravenous volume with increased interstitial fluids [11], and this study revealed that many patients simultaneously had both dehydration and fluid retention symptoms. Therefore, it is suggested that while artificial hydration therapy may help alleviate membranous dehydration signs in some patients, the overall benefits of active hydration therapy are limited by the possibility of aggravating fluid retention symptoms [14, 15].

This study did not identify any beneficial effects of artificial hydration therapy on psychiatric symptoms. Previous retrospective, historical control and prospective observational studies have demonstrated that active rehydration could contribute to alleviation of delirium [12, 13, 16], while another historical control study and a small randomized controlled trial found no overall benefit [7, 27]. These conflicting results suggest that the benefits of artificial hydration therapy in alleviating delirium may be applied to a certain group of patients with specific underlying etiologies, such as opioid hyperexcitability syndrome or acute dehydration [5].

This study identified no clear association between hydration volume and the development of bronchial secretion. Of note was that our sample was limited to patients with abdominal malignancies, and hydration volume was relatively small. Therefore, our findings suggested that, for patients with abdominal malignancies receiving moderate level of hydration (e.g. $\leq$1 l/day), bronchial secretion is not influenced by hydration volume. On the other hand, previous observational studies including lung cancer patients have identified pulmonary edema as a significant etiology of severe bronchial secretion [10, 29], and bronchial secretion has multiple etiologies, including respiratory malignancies, infection, pulmonary edema, dysphasia and brain metastases [30, 31]. Thus, the effect of hydration volume on other groups of patients should be examined in future studies.

This study successfully recruited patients with a narrow range of primary tumor sites, enrolled patients from multiple centers, used a comprehensive set of assessments that were sensitive to symptom changes and highly feasible, and prospectively evaluated multiple symptoms. Nonetheless, this study has several limitations. First, this was not an intervention trial. Although we acknowledge that a randomized controlled study is the best research design to scientifically clarify the treatment effects of hydration therapy, the information required for planning controlled trials, such as useful end point measures, their estimated differences and the necessary sample size, is lacking. Therefore, we decided to perform an observation study first. Secondly, the main end points were measured objectively. Therefore, we did not evaluate the effect of hydration volume on patients' subjective well-being, and there was a possibility of under- or overestimation in addition to reporting bias from treating physicians. This is, we believe, a realistic option to minimize selection bias and ensure sufficient sample size, but this flaw should be overcome in the next study. Future studies should adopt a combination of patient-rated well-being and the objective methods successfully used in this study as the primary end points. Thirdly, the reliability and validity of some measurements (i.e. peripheral edema, ascites and pleural effusion) have not been formally tested. We minimized this potential bias by confirming the full agreement of physicians and nurses, and explicitly defining the criteria in rating systems. Fourthly, stomach cancer is one of the most common malignancies in Japan, and was the primary diagnosis in nearly 30% of our subjects. Our findings therefore may not be generalizable to patients from other countries. Fifthly, as only patients who eventually died were analyzed, we did not evaluate the effects of hydration on patient survival. Finally, the result could be influenced by the treatment bias: it is possible that dehydration symptoms in the non-hydration group would have improved if they had received hydration, or that fluid retention symptoms in the hydration group would have been minimized if they had not received hydration.

In conclusion, although artificial hydration therapy might alleviate membranous dehydration signs in terminally ill patients, it could worsen peripheral edema, ascites and pleural effusions. Our findings suggest that the potential benefits of artificial hydration therapy should be balanced with the risk of worsening fluid retention symptoms. Further clinical studies are clearly needed to identify which subgroups of terminally ill patients may or may not benefit from artificial hydration therapy. In the meantime, an individualized treatment based on the comprehensive assessment followed by close monitoring of both dehydration and fluid retention symptoms is strongly recommended.

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Gastritis Cystica Polyposa Concomitant with Gastric Inflammatory Fibroid Polyp Occurring in an Unoperated Stomach

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Abstract

The endoscopic examination of a 61-year-old male patient revealed a protruding lesion in the greater curvature of the lower third area of the stomach. The lesion, 17 mm in size, was resected completely with endoscopic submucosal dissection using an insulated-tip diathermic knife (IT-ESD). Histological examination of the protruding lesion revealed proliferation of fibroblasts and infiltration of inflammatory cells in the mucosa and submucosa, and it was diagnosed as an inflammatory fibroid polyp (IFP). Gastritis cystica polyposa (GCP) was presented adjacent to the IFP. This may be the first report of GCP concomitant with gastric IFP occurring in an unoperated stomach.
(Internal Medicine 44: 46–49, 2005)

Key words: gastric cysts, inflammatory polyp, neoplasm, insulated-tip diathermic knife, endoscopic submucosal dissection

Introduction

Inflammatory fibroid polyp (IFP) is a relatively rare disorder, which is thought to be clinically and histologically benign, and was first described as "polypoid fibroma" in 1920 by Konjetzny (1). Gastritis cystica polyposa (GCP), characterized by polypoid hyperplasia of the gastric mucosa, is an uncommon lesion that develops in patients who have undergone gastroenterostomy with or without gastric resection (2–5). GCP is rarely found in an unoperated stomach (4–6). There have been no previous case reports of gastric IFP concomitant with GCP. Herein, we report a case of GCP concomitant with gastric IFP occurring in an unoperated stomach, and treated by endoscopic submucosal dissection using an insulated-tip diathermic knife (IT-ESD).

Case Report

A 61-year-old man visited our hospital for further evaluation of abnormal radiographic findings of the stomach in a yearly physical checkup on October 13, 2001. No specific family or past medical history was identified. Routine hematological examination and biochemical tests were within normal limits. Serum anti-*Helicobacter pylori* (*H. pylori*) immunoglobulin G (IgG) antibody was positive. Endoscopic examination of the upper digestive tract revealed a protruding lesion, about 20 mm in diameter, in the pyloric gland area, in the greater curvature of the lower third area of the stomach (Fig. 1). The biopsy specimen obtained from the lesion revealed normal gastric mucosa. We had to make a differential diagnosis between a large hyperplastic polyp and a submucosal tumor covered with normal gastric mucosa. Endoscopic ultrasonography (EUS) with a miniature probe of 20 MHz frequency using the water filling method revealed a hypoechoic mass covered with a hyperechoic lesion that had anechoic areas in the second and third layers of the gastric wall (Fig. 2). This protruding lesion was surrounded by intestinal metaplastic mucosa. There were some red patches with erosions in the antrum, however, there was not any diffuse red area in the fundic area. The culture of gastric mucosa propagated the microaerophilic bacteria, *H. pylori*. On the basis of EUS findings, we could not deny that the tumor might be gastric cancer resembling a submucosal tumor or gastric cancer with a mucinous component. We suspected this patient had a submucosal tumor, but the definite diagnosis could not be made. The patient underwent an IT-ESD for histological confirmation. IT-ESD was performed as we previously described (7). The protruding lesion, 17×15×5 mm in size, was resected completely with a safe lateral

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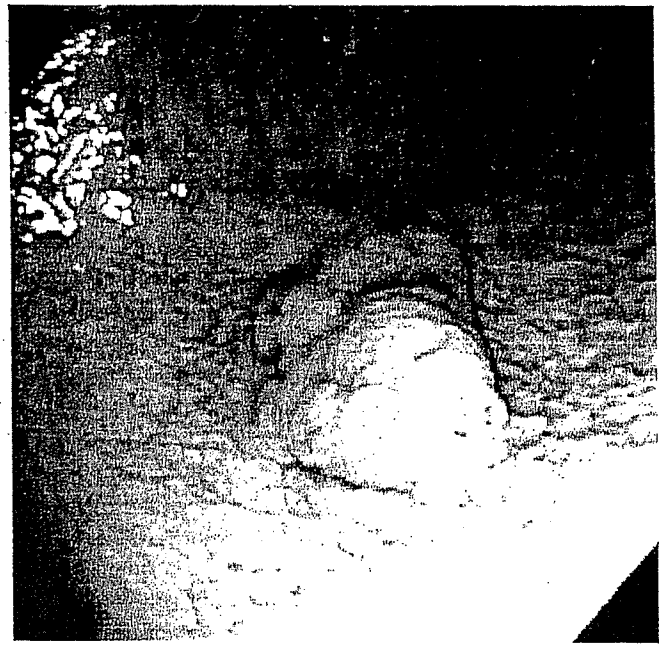

Figure 1. Endoscopic appearance of the elevated lesion in the greater curvature of the lower third area of the stomach. The lesion was covered with normal mucosa.

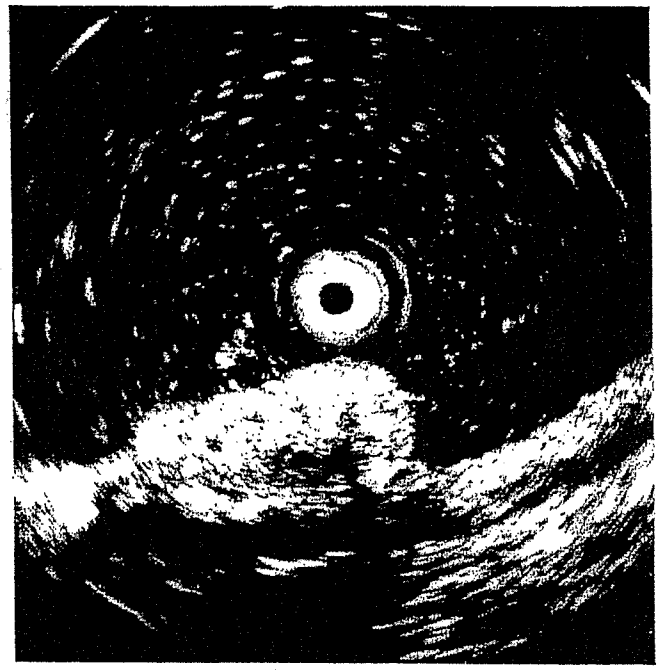

Figure 2. Endoscopic ultrasonography (EUS) revealed that a hypoechoic mass covered with hyperechoic lesion that had anechoic areas interrupted the second and third layers of the gastric wall.

and vertical margin, and resected specimen was 30×22 mm in size (Fig. 3). Histological examination of the protruding lesion revealed that the tumor was distributed from the mucosa to submucosal layer and multiple cysts were adjacent to the tumor (Fig. 4A). The proliferation of fibroblasts and the infiltration of inflammatory cells such as plasma cells and eosinophils were seen in the submucosal tumor (Fig. 4B). This tumor was diagnosed as gastric IFP. The elongation of the gastric foveolae along with hyperplasia and cystic dilatation of the gastric glands were seen (Fig. 4C). The protruding lesion was diagnosed as GCP concomitant with gastric IFP. Histologically, the tumor was surrounded by intestinal metaplastic mucosa. The postoperative course was uneventful. He has been under close periodic observation, and there is no evidence of disease 29 months after IT-ESD.

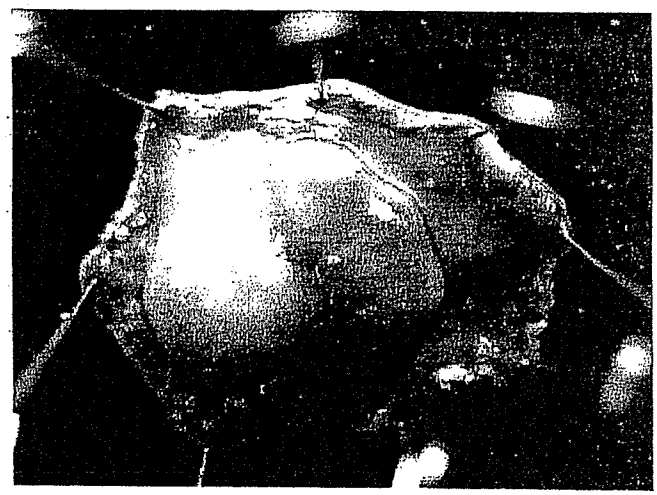

Figure 3. Macroscopic findings of the resected tumor. The resected specimen was 30×22 mm in size and the protruding lesion was resected completely with a safe lateral and vertical margin.

Discussion

IFP is a rare mucosal or submucosal lesion of the gastrointestinal tract that follows a benign course. Most of the fibroids reported were located in the mucosa and submucosa, although Ishikura et al (8) reported six lesions and we also reported one lesion (7) limited to the mucosa. The pathogenesis of IFP remains unknown. Endoscopic findings of IFPs are smooth sessile or pedunculated polyps. The final diagnosis of IFP depends on the pathological findings, however the histological findings of the biopsy specimen are often difficult to diagnose. In the present case, the tumor was completely resected by IT-ESD and the diagnosis of GCP concomitant with gastric IFP was made. This may be the first report of GCP concomitant with gastric IFP.

GCP was first described by Littler and Gleibermann in 1972 (2). It is characterized histologically by elongation of the gastric foveolae along with hyperplasia and cystic

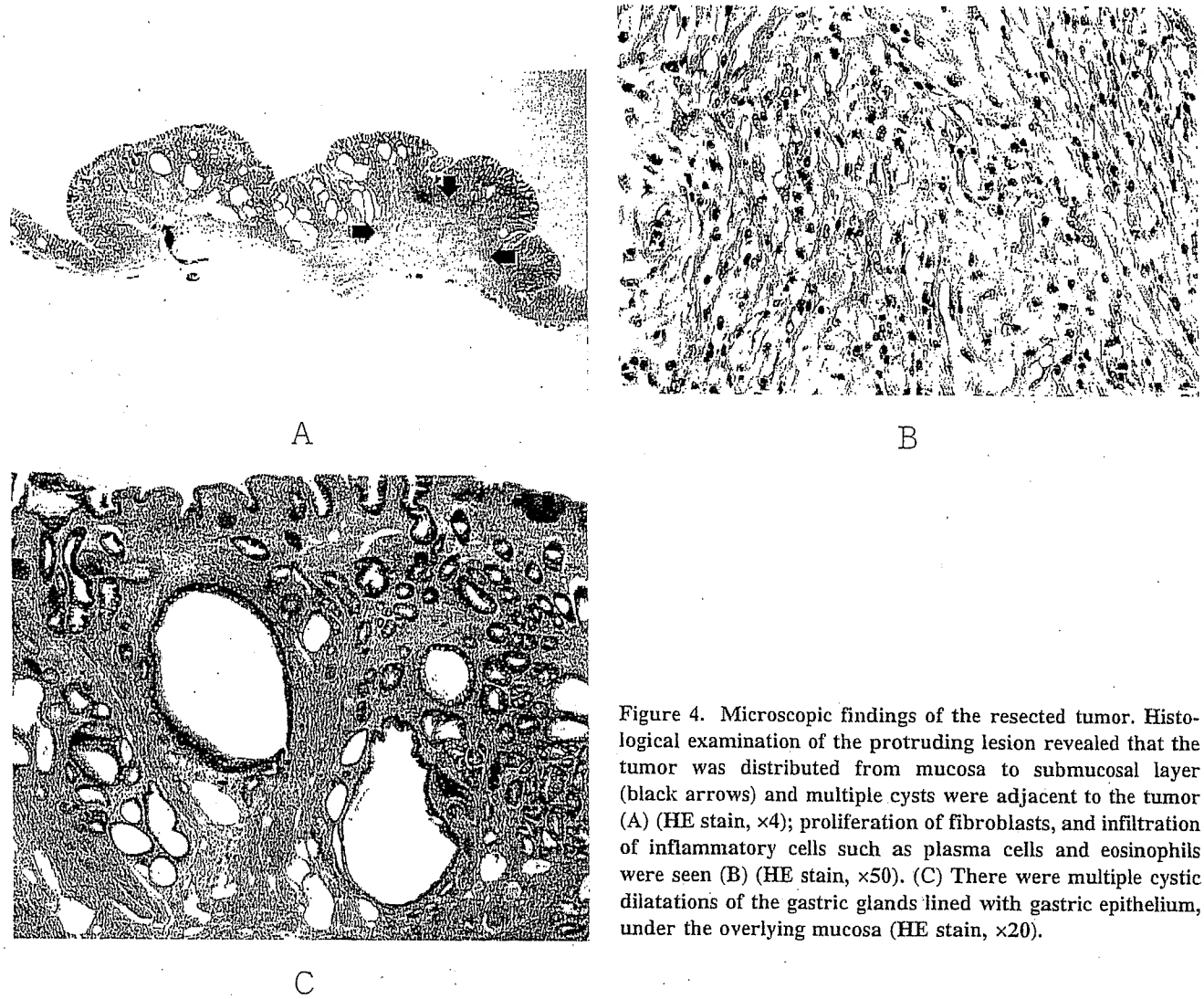

Figure 4. Microscopic findings of the resected tumor. Histological examination of the protruding lesion revealed that the tumor was distributed from mucosa to submucosal layer (black arrows) and multiple cysts were adjacent to the tumor (A) (HE stain, ×4); proliferation of fibroblasts, and infiltration of inflammatory cells such as plasma cells and eosinophils were seen (B) (HE stain, ×50). (C) There were multiple cystic dilatations of the gastric glands lined with gastric epithelium, under the overlying mucosa (HE stain, ×20).

dilatation of the gastric glands extending into the gastric submucosal layer (2–6). These lesions are usually found at the gastroenterostomy sites, presumably because of increased mucosal mobility accompanying peristaltic contractions and repair of the preanastomotic gastric mucosa after damage caused by reflux of duodenal contents (2, 9, 10). Koga et al described that there were 4 cases of GCP (9.5%) in their 42 patients who had once undergone gastrojejunostomy and received further surgery on account of various reasons (9). In Japan, there are many reports describing the association of GCP with early or small cancerous lesions in the remnant stomach (11, 12). Thus GCP has been proposed to be a possible precancerous lesion itself (13). GCP may rarely also develop in an unoperated stomach as in the present case. GCP in an unoperated stomach frequently occur in the gastric fundus (4–6). However, few cases with GCP in an unoperated stomach have been reported and further analysis of many cases is necessary in the future. GCP in an unoperated stomach has generally been assumed to be of congenital origin, mainly because of the lack of documented prior gastric ulceration or trauma (5, 14). However, the pathogenesis of GCP in an unoperated stomach is not clear. Thus further studies on the pathogenesis of GCP in an unoperated stomach are certainly necessary.

The pathogenesis of IFP remains unknown, however, some authors have proposed that IFP is caused by an allergic reaction to an inflammatory stimulus such as bacterial, chemical, traumatic, etc, or is a reactive lesion of fibroblastic or myofibroblastic nature (15). Gastric IFP frequently appears in the antrum (7), and the incidence of gastric IFP was reported to be 3.1% of one series of 5,515 gastric polyps by Stolte et al (16). Recently, Nishiyama et al (17) reported a case of IFP that morphologically changed after the *H. pylori* eradication therapy. They claimed that factors derived from gastric epithelial cells in response to *H. pylori* infection, such as inflammatory cytokines and growth factors, might affect the growth of IFPs. Their opinion is not proved although there is another report describing the relation between IFP and *H. pylori* infection (18). It is interesting that their report suggests the relationship between gastric IFP and *H. pylori*.

We could speculate possible pathogenetic relationships of gastric IFP with GCP as follows: 1) GCP occurs via stimulation of IFP and 2) IFP and GCP arise independently. The present case may indicate that some common factors are involved in the etiology of IFP and GCP, though there is no direct evidence at present. On the supposition, one of the factors may be *H. pylori*. However, there have been no reports describing the relationship between GCP and *H. pylori*. Further studies on the relationship between IFP and GCP are certainly necessary. The present case does not have direct evidence that IFP is related to GCP, however, we thought it would be valuable to report this case, since this may be the first report of GCP concomitant with gastric IFP occurring in an unoperated stomach. However, it is likely that there are latent patients with GCP concomitant with gastric IFP occurring in an unoperated stomach, which might be discovered by endoscopic resection in the future. Because both gastric IFP and GCP in an unoperated stomach are benign tumors and they are seldom resected by endoscopic resection or surgery.

The IT-ESD is a useful new endoscopic mucosal resection (EMR) method, which recently has been widespread in Japan. It is difficult to remove a complete tumor larger than 10 mm in diameter in one-piece by the usual strip biopsy method. However Ohkuwa et al (19) reported a one-piece resection rate of IT-ESD (between 11 and 20 mm) of 75% in 16 patients with adenocarcinoma or adenoma. As to the endoscopic treatment of gastric IFP, Nishio et al (20) reported a case of gastric IFP who revealed an increase in size of the IFP after incomplete endoscopic resection within a year. Thus, gastric IFP should be resected completely with a safe margin if EMR is performed. The lesion in the present case was about 20 mm, however, the result of IT-ESD was that we could resect this tumor completely and ensure a safe margin. Here, IT-ESD was an effective and safe therapy for a gastric protruding lesion of nearly 20 mm in diameter.

In conclusion, we report the first case of GCP adjacent to gastric IFP occurring in an unoperated stomach. The IT-ESD was a useful treatment method for GCP concomitant with IFP in the present case. There have been no previous case reports of GCP concomitant with gastric IFP. This case emphasizes that it is important to keep in mind that gastric IFP might be accompanied by GCP in an unoperated stomach though such a condition is extremely rare.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Nationwide Survey on Complementary and Alternative Medicine in Cancer Patients in Japan

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ABSTRACT

Purpose
To determine the prevalence of use of complementary and alternative medicine (CAM) by patients with cancer in Japan, and to compare the characteristics of CAM users and CAM nonusers.

Patients and Methods
A questionnaire on cancer CAM and the Hospital Anxiety and Depression Scale were delivered to 6,607 patients who were treated in 16 cancer centers and 40 palliative care units.

Results
There were 3,461 available replies for a response rate of 52.4%. The prevalence of CAM use was 44.6% (1,382 of 3,100) in cancer patients and 25.5% (92 of 361) in noncancer patients with benign tumors. Multiple logistic regression analysis determined that history of chemotherapy, institute (palliative care units), higher education, an altered outlook on life after cancer diagnosis, primary cancer site, and younger age were strongly associated with CAM use in cancer patients. Most of the CAM users with cancer (96.2%) used products such as mushrooms, herbs, and shark cartilage. The motivation for most CAM use was recommendation from family members or friends (77.7%) rather than personal choice (23.3%). Positive effects were experienced by 24.3% of CAM users with cancer, although all of them received conventional cancer therapy concurrently. Adverse reactions were reported by 5.3% of cancer patients. CAM products were used without sufficient information by 57.3% of users with cancer and without a consultation with a doctor by 60.7% of users.

Conclusion
This survey revealed a high prevalence of CAM use among cancer patients, without sufficient information or consultation with their physicians. Oncologists should not ignore the CAM products used by their patients because of a lack of proven efficacy and safety.

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INTRODUCTION

The WHO defines complementary and alternative medicine (CAM), or so-called traditional medicine, as follows: "a comprehensive term used to refer both to traditional medical systems such as traditional Chinese medicine, Indian ayurveda and Arabic unani medicine, and to various forms of indigenous medicine."[1] CAM therapies include medication therapies (which involve the use of herbal medicine, animal parts, and/or minerals) and nonmedication therapies carried out primarily without the use of medication (such as acupuncture or manual therapy). Populations throughout Africa, Asia, and Latin America use traditional medicine to help meet their primary health care needs. In addition to being accessible and affordable, traditional medicine is also often part of a wider belief system, and is considered integral to everyday life and well-being. In Europe and North America, CAM is increasingly being used in parallel to

allopathic medicine, particularly for treating and managing chronic disease. Concerns about the adverse effects of chemical medicines, a desire for more personalized health care, and greater public access to health information fuel the increasing use of CAM in many industrialized countries.[2-5]

The widespread use of a variety of nutritional, psychological, and natural medical approaches as CAM has been well documented.[2,6-8] Recent surveys demonstrate that more than 50% of US cancer patients use CAM therapies at some point after their diagnosis.[3,6,7] Despite extensive use, there is a paucity of data available to indicate whether these practices are efficacious and safe.[9-11] Therefore, serious research efforts are underway to determine the scope of CAM use by patients and their motivations for its use.[6-10] CAM in cancer medicine seems to be widely available in Japan as well as in the Western countries. We performed a preliminary survey on cancer CAM in a single cancer center in 1999. This survey revealed that 32% of cancer patients used CAM, and the most frequently used CAM involved natural products, such as mushrooms, shark cartilage, and beeswax-pollen mixtures.[12] The most pressing and significant problems associated with these products were commonly held but incorrect assumptions and the absence of any regulatory oversight. In addition, interactions between herbs and drugs may increase or decrease the pharmacologic or toxicologic effects of either component. For example, St John's wort has recently been reported to dramatically reduce plasma levels of SN-38 (the active metabolite of irinotecan, a key oncologic drug), which may have a deleterious impact on treatment outcome.[13]

An enormous amount of unreliable information on cancer CAM is available from the Internet and other media sources. It is often the case that cancer patients and their relatives are at a loss about how to deal with such information and have a difficult time choosing what kind of CAM they should adopt. However, there have been no large-scale surveys of this sort in Asia, and the actual state of CAM use in cancer patients is still unclear. Therefore, we performed a nationwide cross-sectional survey to evaluate the prevalence of CAM use in cancer patients and their perceptions of cancer CAM, especially of CAM products used in Japan.

PATIENTS AND METHODS

Participants

Before initiation of this survey, the study protocol was examined by the institutional review boards of cancer centers and related hospitals (CCs) joining the nationwide association of medical centers for cancer and adult diseases in Japan, and hospice and palliative care units (PCUs) joining the Japanese association of palliative care. Sixteen of 29 CCs and 40 of 88 PCUs approved the survey. All participating institutions agreed not to treat patients systematically with any CAM. The total number of questionnaires that would be distributed to the patients was predicted by the responsible physician working for each collaborating institute, and this information was provided in advance to the National Shikoku Cancer Center. Questionnaires on cancer CAM were then sent to the responsible collaborating physicians in the CCs and PCUs from October 2001 to March 2002. The day on which the questionnaires were distributed to the patients was determined voluntarily by each institute within 2 weeks of receipt. Questionnaires were distributed to the patients by the medical staff (physicians, nurses, clerks, and so on) at each collaborating institute after exclusion of those with an Eastern Cooperative Oncology Group performance status of 4 and those who underwent surgery that day. Replies were sent back to the National Shikoku Cancer Center directly from each patient. Questionnaires were marked in advance to identify the type of clinic the patients were attending (ie, CCs or PCUs, and inpatient or outpatient). Returned questionnaires were coded with an identification number to ensure confidentiality.

Questionnaire

We had previously evaluated a questionnaire about cancer CAM in 219 cancer patients who were admitted to the National Shikoku Cancer Center as a preliminary study.[12] In the present study, we used a modified version of that questionnaire after testing several samples. Some additional questions were quoted from previously published articles.[6-8] The original questionnaire we used was written in Japanese. The attached questionnaire (Appendix) has been translated into English. The questionnaire was developed through a systematic literature review and discussions by two experienced medical oncologists, a psychiatrist, a pharmacist, a basic scientist, and a research assistant. On the cover page of the questionnaire, CAM was clearly defined as follows: "any therapy not included in the orthodox biomedical framework of care for patients. CAM means remedies that are used without the approval of the relevant government authorities, such as the Ministry of Health and Welfare in Japan, that approve new drugs after peer review of preclinical experiments and clinical trials regulated by law. CAM usually skips these steps and is offered directly to the public. Health insurance does not usually cover the cost of CAM, and patients will be liable for the whole expense incurred by any CAM. CAM includes natural products from mushrooms, herbs, green tea, shark cartilage, other special foods, megavitamins, acupuncture, aromatherapy, massage, meditation, and so on."

The questionnaire was composed of the following two parts: background of the patients (disease, onset, age, sex, daily living activity level, educational level, religion, cancer treatment, changes of outlook on life, satisfaction with receiving conventional medicine, and use of cancer CAM; questions 1 to 12) and users' perception of cancer CAM (initiation time, kinds of CAM used, reason for starting CAM, method of obtaining information about the CAM used, expectations for CAM use, effectiveness or ineffectiveness, adverse effects, average expense per month, whether a history of CAM use was provided to the physician in charge, whether the physician in charge was consulted, response of physician, reason for not consulting physician, and concurrent use of anticancer drugs and CAM products that are sold over the counter; questions 13 to 28).

Hospital Anxiety and Depression Scale

A brief scale, the Hospital Anxiety and Depression Scale (HADS), was used in this study to clarify the relationship between emotional state and CAM preference. The HADS has 14 items in two question groups, one each on anxiety and depression, and each question is rated from 0 to 3. The validity and reliability of the Japanese version of HADS have been confirmed previously.[14,15] From previous articles, including the original one and studies in the Japanese population, we adopted 10 points as the cutoff above which anxiety and depression would be scored as high.[14-16] The patients in the high group were considered to have an adjustment disorder or more severe condition. The HADS was delivered to patients along with the questionnaire on CAM.

Statistical Analysis

Differences of CAM use within categories of selected demographic and clinical variables (age, sex, disease sites, daily living activity level, patient's desire, changes of outlook on life, institute, education, and religion) were assessed by the χ^2 test. The factors predicting CAM use were analyzed by univariate analysis and then multiple logistic regression analysis was performed using all significant predictor variables ($P < .05$). The analysis provided an odds ratio and 95% CI for each variable while simultaneously controlling for the effects of other variables. Variables not contributing substantially to the model were systematically removed in a backward stepwise regression process using the likelihood ratio test as the criterion for removal. The Hosmer-Lemeshow χ^2 test was used to assess the goodness of fit between the observed and predicted number of outcomes for the final model, with $P > .05$ indicating a good fit. All analyses were performed using SPSS Base and Regression models 11.0J (SPSS Japan Inc, Tokyo, Japan)

RESULTS

Response Rate to Questionnaire and CAM User Rates

A total of 6,607 questionnaires on cancer CAM were sent to collaborating CCs and PCUs according to the required number estimated by the primary investigators at those institutes. As a result, questionnaires were delivered to 6,074 patients who were treated in CCs (2,688 inpatients and 3,386 outpatients) and to 533 patients who were treated in PCUs (367 inpatients and 166 outpatients). A total of 3,733 questionnaires were returned to our center, of which 3,461 were valid with useable answers. The remaining 272 returned questionnaires were invalid because of a critical lack of major answers, such as unwritten diagnosis or no response to CAM use. Consequently, the rate of valid replies was 52.4%. Of the valid replies, 3,100 were from cancer patients and 361 were from noncancer patients with benign tumors. The flow diagram of the study population is indicated in Figure 1.

The prevalence of CAM use in cancer patients was 44.6% (1,382 of 3,100) and that in noncancer patients was 25.5% (92 of 361). In terms of background differences, noncancer patients were younger, had less impaired daily activity, and were much more likely to be in CCs than cancer patients. The rate of use among cancer patients was significantly higher than that for noncancer patients ($P < .0001$). All of the 3,100 replies from cancer patients were subject to analysis. Many users (86.7%) started CAM after their diagnosis of cancer and 73.3% of users were continuing it at the time of the survey.

Backgrounds of Patients and CAM Users

The backgrounds of all the cancer patients and CAM users with cancer are summarized in Table 1. The prevalence of CAM use was significantly higher in patients who were younger than 61 years old ($P < .0001$), female ($P < .0001$), patients with a lower daily activity level ($P < .0001$), patients with higher education ($P < .0001$), patients who received chemotherapy ($P < .0001$), patients with a change of outlook on life ($P < .0001$), patients who were dissatisfied with conventional treatments ($P = .0001$), patients in PCUs ($P < .0001$), and patients with a low HADS anxiety score

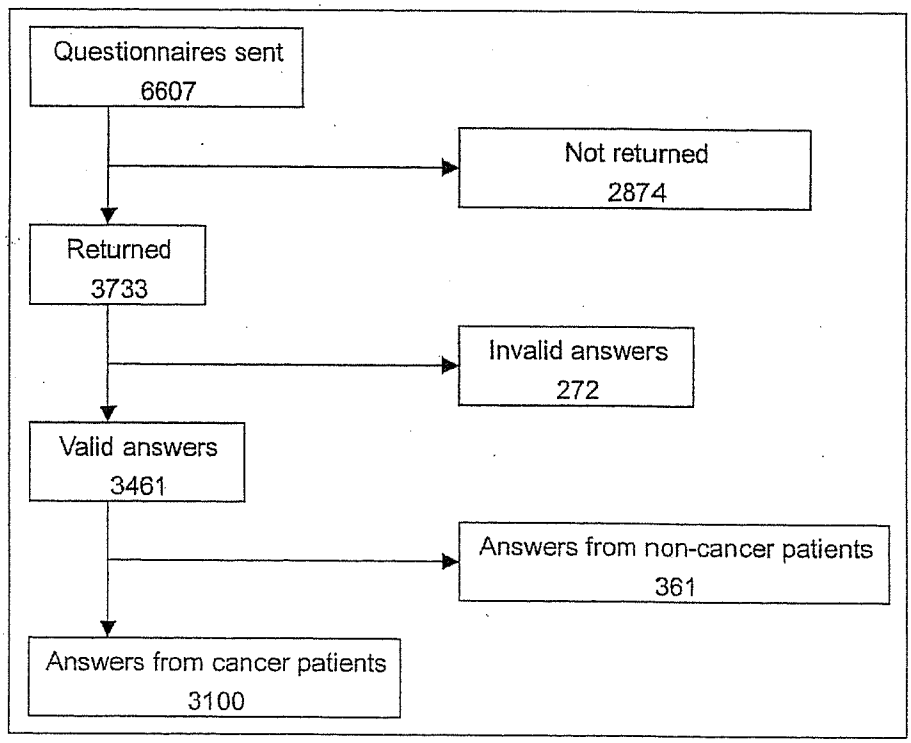

Fig 1. Flow diagram of the study population.

Table 1. Background and CAM Usage

Background	No. of Patients	No. of Users	%	P (χ^2 test)
Total	3,100	1,382	44.6	
Age, years				
> 60	1,603	625	39.0	
≤ 60	1,485	752	50.6	< .0001
Sex				
Male	1,484	586	39.5	
Female	1,614	796	49.3	< .0001
Activity of daily living				
Free or somewhat limited	2,293	1,002	43.7	
Bed rest (≥ 50% of each day)	726	348	47.9	< .0001
Education				
High school	1,721	719	41.8	
Post–high school	879	464	52.8	< .0001
Practicing religion				
No	2,140	945	44.2	
Yes	593	281	47.5	.1660
Conventional treatment				
Chemotherapy	1,839	966	52.6	
Nonchemotherapy	1,260	414	32.9	< .0001
Change in outlook on life				
No	1,381	509	36.9	
Yes	1,558	793	50.9	< .0001
Treatment met patient's needs				
No	1,212	591	48.8	
Yes	1,830	762	41.7	.0001
Institute				
Cancer centers	2,811	1,203	42.8	
Palliative care units	289	179	61.9	< .0001
Treatment place				
Inpatient ward	1,665	717	43.1	
Outpatient clinic	1,434	665	46.4	.0699
HADS				
High anxiety score (≥ 11)	1,915	852	44.5	
Low anxiety score (< 11)	741	378	51.0	.0029
High depression score (≥ 11)	1,018	510	50.0	
Low depression score (< 11)	1,652	734	44.4	.0049
Cancer				
Lung	380	203	53.4	
Breast	532	273	51.3	
Hepatobiliary	256	129	50.4	
Genitourinary	445	195	43.9	
Gastrointestinal	708	278	39.3	
Head and neck	266	82	30.8	
Other	513	222	43.3	< .0001

Abbreviations: CAM, complementary and alternative medicine; HADS, Hospital Anxiety and Depression Scale.

($P = .0029$) and a high HADS depression score ($P = .0049$). In terms of disease sites, the rate of use was higher in patients with lung, breast, and hepatobiliary cancers than in those with other cancers ($P < .0001$). The prevalence of CAM use in inpatient wards of CCs and that in outpatient clinics of CCs was 40.6% and 45.3%, respectively. The prevalence of CAM users in inpatient wards of PCUs and that in outpatient clinics of PCUs was 61.0% and 64.3%, respectively. The prevalence of CAM use in PCUs was significantly higher than that in CCs in outpatient clinics ($P < .0001$), as well as inpatient wards ($P < .0001$). Similarly, the prevalence of CAM use in inpatient wards was significantly higher than that in outpatient clinics in both CCs ($P < .0001$) and PCUs ($P < .0001$).

Predictors of Cancer CAM Use

Multivariate logistic regression analysis was performed to detect the factors predictive of CAM use, using the variables with a significantly different rate among users. The institutional review board of one CC did not permit the questions about education and religion, and 500 questionnaires in which those two questions were deleted were sent to that center. As the result, the rate of reply on education and religion was apparently low. Given that the anxiety and depression scores of HADS could not be calculated if one of each of seven questions was not answered, the number of available replies was also decreased relative to the other questions. For these reasons we performed two analyses of

the relevant variables separating the two patient populations: analysis 1 included the significant variables other than education and HADS, and analysis 2 included all significant variables as shown in Table 2. Patients who received chemotherapy; patients in PCUs; patients whose outlook on life had changed; patients with lung, breast, or hepatobiliary cancer; patients younger than 61 years old; and female patients were more likely to use CAM in both sets of analysis. In analysis 2, higher education was determined as a potent predictive factor, and dissatisfaction with conventional treatments was a weak predictive factor.

Types of CAM

The types of CAM used are listed in Table 3. The majority of CAM users (96.2%) relied on CAM products as opposed to nonmedical therapies. The most frequently used CAM product was mushrooms (Agaricus 60.6% and active hexose correlated compound [AHCC] 8.4%). Agaricus is extracted from a particular type of mushroom, *Agaricus blazei Murill*. It is purported to be an interferon inducer. AHCC is thought to act as an immunomodulator. Other CAM products were propolis (28.8%), Chinese herbs (7.1%), chitosan (7.1%), and shark cartilage (6.7%). Propolis is a beeswax-pollen mixture. Chitosan is an extract from crustaceans, such as crabs and lobsters. These are claimed to be enhancers of the immune system. Shark cartilage is known to be an inhibitor of tumor angiogenesis.[17] Chinese herbs (easily bought over the counter, but not prescribed by physicians) were used by 7.1% of patients. The rate of use of traditional Chinese medicine (qigong, moxibustion, and acupuncture) was less than 4%.

Perceptions and Attitudes Toward CAM

As shown in Table 3, 77.7% of the patients started using CAM on recommendation from family members or friends. Only 23.3% of the patients decided to use CAM on the basis of their own will. Patients expected the following effects from CAM: suppression of tumor growth (67.1%), cure (44.5%), symptom relief (27.1%), and complementary effects to conventional therapy (20.7%). In terms of the effectiveness of CAM, 24.3% of the patients experienced positive effects, such as tumor shrinkage, inhibition of tumor growth, pain relief, fewer adverse effects from anticancer drugs, and feeling better. However, at the same time, all of the patients were treated with conventional therapies such as surgery, chemotherapy, hormonal therapy, and/or radiation. The effects were not related to the use of any specific CAM product. Almost two thirds of the patients did not know if the CAM really worked or not. Conversely, only 5.3% of the patients experienced adverse effects, such as nausea, diarrhea, constipation, skin eruption, and liver dysfunction. No adverse effects were experienced by 62.2% of the patients. Patients who were uncertain about adverse effects comprised 32.6% of respondents.

More than half of the patients (57.3%) started CAM without obtaining enough information on it. Most of the patients (84.5%) had not been asked about CAM use by their physician or other health professionals. Nearly two thirds of the patients (60.7%) have never consulted their physicians on CAM use. When the patients consulted their physicians, 60.3% of the patients were told that they were free to use it or not. Patients who were told to continue using CAM and those who were told to cease use comprised 10.5% (8.5% in CCs and 19.5% in PCUs) and 11.3% (12.2% in CCs and 7.3% in PCUs) of CAM users, respectively. The main reason (56.1%) given for why they were not willing to ask their physicians about CAM was that their physicians did not ask about CAM use. The prevalence of patients who thought the physicians would not understand CAM and who thought they would prohibit CAM use was 19.4% and 8.7%, respectively.

The prevalence of concurrent use of anticancer drugs and CAM products was 61.8% in CAM users. The average monthly expenditure for CAM was 57,000 yen (approximately US $500; range, 0 to 1200,000 yen).

Table 2. Analysis of CAM Use With Multivariate Logistic Regression

Variable (reference)	Analysis 1 (n = 2,810)*			Analysis 2 (n = 2,020)†		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Used chemotherapy (*v* did not)	2.06	1.75 to 2.43	< .0001	2.24	1.86 to 2.73	< .0001
Seen at a palliative care unit (*v* a cancer center)	2.29	1.73 to 3.03	< .0001	2.22	1.59 to 3.10	< .0001
Experienced a change in outlook on life (*v* did not)	1.47	1.25 to 1.73	< .0001	1.40	1.15 to 1.70	.0007
Lung, breast, hepatobiliary cancer (*v* other cancers)	1.47	1.25 to 1.73	< .0001	1.34	1.10 to 1.62	.0031
≤ 60 years of age (*v* > 60 years)	1.38	1.16 to 1.64	< .0001	1.32	1.08 to 1.61	.0055
Symptomatic (*v* asymptomatic)	1.16	0.98 to 1.36	.074	1.23	1.01 to 1.49	.0373
Did not meet patient's needs (*v* met them)	1.21	1.03 to 1.42	.0234	1.22	1.00 to 1.48	.047
Female (*v* male)	1.17	0.98 to 1.40	.0764	1.16	0.94 to 1.43	.174
More educated (*v* less educated)	—	—	—	1.61	1.32 to 1.95	< .0001
Low HADS score for anxiety (*v* high score)	—	—	—	1.11	0.90 to 1.38	.3227
High HADS score for depression (*v* low score)	—	—	—	1.02	0.84 to 1.25	.8447

Abbreviation: HADS, Hospital Anxiety and Depression Scale.
*Analysis 1 was performed with all variables except for education and HADS because there were fewer responses for these variables.
†Analysis 2 was performed with all variables listed.

Table 3. Types of CAM Used and Perceptions and Attitudes of 1,382 CAM Users

Characteristic	%
Type of CAM used*	
CAM products (Chinese herbs, mushrooms, shark cartilage, vitamins, and so on)	96.2
Qigong†	3.8
Moxibustion	3.7
Acupuncture	3.6
Motive for starting CAM	
Recommendation from family or friends	77.7
Will of patients themselves	23.3
Expectations for CAM use*	
Suppress cancer growth	67.1
Cure	44.5
Symptom relief	27.1
Complementary effects to conventional therapy	20.7
Positive effects	
Yes	24.3
No	6.2
Unclear	69.5
Adverse effects	
Yes	5.3
No	62.2
Unclear	32.6
Obtained enough information on CAM	
Yes	42.7
No	57.3
Heard about CAM use from health professionals	
Yes	15.5
No	84.5
Consulted with doctors about CAM use	
Yes	39.3
No	60.7

NOTE. Unanswered rates were less than 10% in all categories.
*Questions in which multiple selections of answers were allowed.
†Component of traditional Chinese medicine that combines movement, meditation, and regulation of breathing to enhance the flow of vital energy (qi) in the body to improve circulation and enhance immune function.

DISCUSSION

The surveyed cancer population in this study used complementary but not alternative therapies because they were simultaneously treated in conventional medical facilities. However, we could not completely rule out the possibility that they had previously used alternative medicine. Therefore, we used the term CAM in this study.

Although we received more than 3,000 replies, the response rate (52.4%) was a little lower than in previous studies.[3,6,18,19] This may have introduced bias into our study. However, the patients' privacy was completely preserved and our survey method was the easiest way for the patients to reply to the questionnaire without feeling any pressure. We believe that our survey is helpful for assessing regional research priorities and for comparing the current status of CAM use in studies using a similar mailed-questionnaire method in other countries.

The prevalence of CAM use in cancer patients was significantly higher than that in noncancer patients. Most of the noncancer patients in this study had benign tumors and attended the cancer centers. Therefore, the noncancer patients in our study represent neither the general healthy population nor patients with benign chronic disease. Indeed, the rate of CAM use in the general population of people suffering from disease in our country was reported to be higher than that of our noncancer patients.[20] The prevalence of CAM use in cancer patients was 44.6%. This rate was slightly higher than that found in our previous study (32%) of a single cancer center survey.[12] The prevalence appears to increase each year in our country, as in the Western countries.[2] CAM user rates were significantly higher in patients undergoing chemotherapy and in patients in PCUs, and these associations were confirmed by multivariate analysis. Chemotherapy is usually delivered to inoperable, advanced, or metastatic cancers with a palliative intent but not a curative intent. In PCUs, there were no conventional treatments with tumor shrinkage as the expected outcome. Patients' relatives or friends often recommended that the patient use CAM products in that situation. In general, medical professionals in PCUs are rather generous in accepting the use of CAM. The percentage of patients whose CAM use had been recommended was approximately two-fold higher in PCUs (19.5%) compared with that in CCs (8.5%). These are probably the primary reasons for the high rate of CAM use in patients undergoing chemotherapy and in PCUs. The multivariate analysis also revealed a close association between CAM use and high educational status, changes in outlook on life, primary cancer site, and younger age. The patients' perception of received conventional treatments and female sex were marginal predictors in our study. Predictors of CAM use have been reported in many previous studies,[7,8,19] and our data support that these predictors are similar to those in developed countries. With few exceptions, the literature indicates that highly educated patients and younger patients tend to use CAM.

Different predictors are associated with the different types of CAM used. In our surveyed population, the most frequently used CAM was natural products. Oral intake of medications is more likely in patients with lung, breast, and hepatobiliary cancers than in patients with head and neck, GI, and urogenital cancers, taking the sites of disease and the manners of progression into consideration. This is likely to be closely related to the use of CAM products because all of these are oral supplements. The predictors chemotherapy and disease site would therefore be related to the type of CAM used (ie, CAM products). Indeed, this hypothesis was suggested in a previous report in which predictors shifted to include chemotherapy after spirituality and psychotherapy or support groups were excluded from the types of CAM used.[7] Supplements (herbs or vitamins) were the main types of CAM used by the patients of that limited analysis. Unexpectedly, psychological factors such as anxiety and depression showed no relation to the use of CAM. However, these factors frequently fluctuate during the disease course, as we observed in the process of informed consent.[15] If the HADS had been administered when the patients initiated CAM use, the results would likely be different.

The majority of CAM users in this study took products such as mushrooms, herbs, and shark cartilage. Mushrooms (Agaricus and AHCC) were the most frequently used among the products. This was characteristic of our CAM users. The popular types of CAM in Western countries, such as spiritual practice, mind and body therapy, vitamins and special diet, and homeopathy, were rarely used in our country. Such mushrooms are sold in Japan as diet supplements. The providers emphasize their effects on boosting the immune system based on basic experimental findings using cultured human tumor cells, and advertise in many magazines or through the Internet with anecdotal reports of users. No reliable, well-designed clinical trials in cancer patients have been performed with these mushrooms. Nonetheless, many cancer patients used such products hoping for tumor growth suppression (67.1%) and cure (44.5%) rather than complementary effects (20.7%). These mushrooms and other similar natural products are generally expensive. This contributed to the high expenditure on CAM among our users (US $500 per month on average), compared with that in the Western countries (US $50 to $70 per month on average).[6] The main motive for CAM use was the recommendation of family members or friends. The population of patients who were willing to seek out CAM on their own was unexpectedly small, about one fourth of the users. It has been reported that support group dynamics influence individuals to be more likely to use CAM among breast cancer survivors.[6] In our study, many patients seemed to be motivated to use CAM by the recommendations of relatives. Friends also offered recommendations on CAM use.

Approximately one fourth of the users experienced positive effects from CAM, even though they all received conventional therapies previously or concurrently. Although it was unclear whether the positive effects were due to the CAM products or the conventional treatments, they nonetheless believed that the CAM was effective. In retrospect, we should have added a question to our questionnaire about the effectiveness of the conventional treatments received. Conversely, most patients reported no adverse reactions to CAM. However, the potential for harmful drug–CAM product interactions exists.[21-23] Herbs or vitamins can mask or distort the effects of conventional drugs.

This survey revealed that approximately 60% of users started CAM without obtaining enough information about it, and without informing their doctors. This proportion was similar to that in our previous survey.[12] The same issues have been pointed out in many reports from the United States and Europe.[7,24,25] In our survey, when patients consulted their physicians, 60.3% of the patients were told that they were free to continue using CAM or to stop, whereas 10.5% of the patients were told to continue using CAM and 11.3% of the patients were told to stop. These figures were also similar to the results in our previous study of clinical oncologists.[26] When oncologists were asked, 74% of them neither recommended nor prohibited the use of the products. Twelve percent of them encouraged their patients to use CAM products, and 6% told their patients to stop. It appears that a difficult situation for many oncologists emerges because of the lack of scientific information on CAM. However, physicians should acknowledge that the main reason (56.1%) patients did not inform their physicians of their CAM use was that the physicians did not ask them about it. These results indicate that better patient-physician communication and more reliable information on CAM products are needed. The prevalence of concurrent use of anticancer drugs and CAM products was considerably high (61.8%) in the present study. In our previous survey of oncologists, 83.9% of oncologists had administered anticancer drugs concurrently with CAM products.[12] Nevertheless, our present knowledge of interactions is incomplete, especially regarding anticancer drugs.[22,23] More research is urgently needed. Oncologists should be aware of these facts, and the use of CAM products should be determined before initiating chemotherapy, especially when using new investigational drugs.

A few limitations of this study must be acknowledged. First, the response rate was somewhat low compared with that of other studies, although it was greater than 50%, as discussed previously. Second, there is no definite evidence that our study population is representative of cancer patients in Japan. It seems impossible to select cancer patients randomly from throughout the entire country. We used the associations of CCs and PCUs in Japan as our survey source. Otherwise, such a large-scale survey could not be performed. These limitations have also been reported in the previous literature,[7,8] and unfortunately, inconsistencies in measures of CAM and differing patient populations and methodologies (ie, interviews *v* mailed surveys) limit the generalization of studies on CAM use.[3,4] Third, two questions were deleted from the questionnaire sent to one of the CCs. As a result, about 500 replies on education and religion were lacking. However, the analyses with or without the data from that center achieved similar results. Therefore, this did not significantly affect our conclusions.

Many cancer patients continue receiving oncologic care with standard therapies while pursuing CAM methods. A recent survey regarding the impact of the media and the Internet on cancer patients revealed that 71% of cancer patients actively searched for information, and 50% used the Internet.[27] The survey concluded that strategic efforts were needed to provide guidance for patients to help them better interpret such medical information. Oncologists need to be aware of the importance of this issue and of the rationale used to promote CAM. A great need for public and professional education regarding this subject is evident.

Acknowledgment

We thank all of the physicians and patients who participated in this survey.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix

1. What is your disease?

_____

2. When was your disease diagnosed?

Year _____ month _____

3. How old are you?

_____ Years old

4. Please indicate your sex.

Male/Female

5. What about your present daily activity? Please tick the number below.

1) not limited at all, 2) somewhat limited with slight symptoms

3) bed rest more than 50% of the day, 4) bed rest all day

6. Please indicate your level of education.

1) junior high school, 2) high school, 3) college, 4) university, 5) other ( )

7. Are you committed to any religion?

Yes / No

8. Please indicate all treatments that you have received.

1) surgery, 2) chemotherapy, 3) hormonal therapy, 4) radiation, 5) palliative care

6) others ( )

9. Please indicate all treatments that you are currently receiving or will receive.

1) surgery, 2) chemotherapy, 3) hormonal therapy, 4) radiation, 5) palliative care

6) others ( )

10. Has your outlook on life been changed by suffering from this disease?

Yes / No (if yes, how?)

11. Did (Do) the treatments you received meet your needs?

Yes / No

12. Have you ever used complementary and alternative medicines (CAM)?

(*CAM includes various therapies as follows: Chinese herbal medicine, other CAM products such as Agaricus, Propolis, Chitosan, and shark cartilage, acupuncture, chiropractic, aromatherapy, homeopathy, imagery, yoga, thalassotherapy, hypnosis, etc.)

Yes / No

If 'yes', please continue to answer the questions below.

If 'no', the questions are finished here. Thank you very much for your cooperation.

---

13. When did you start CAM?

Year _____ month _____

14. Are you using CAM now?

Yes / No (if no, when did you stop? Year _____ month _____)

15. What kind of CAM do (did) you use?

(continued on following page)

Appendix (continued)

Please state all the names of cancer CAM you use (used), referring to cancer CAM notes*.

_____ _____

_____ _____

_____ _____

16. Why did you start CAM? Please tick the number below.

1) recommended by family members or friends, 2) your own free will,

3) recommended from a physician, 4) other ( )

17. Did you obtain enough information about the efficacy and safety of CAM before you started it?

Yes / No

18. What did (do) you expect by using CAM? Multiple choices are allowed in this question.

1) cure, 2) suppress the progression, 3) improve the symptoms, 4) complementary effects to the present medicine, 5) other ( )

19. Did it work?

Yes / No / difficult to judge

20. If 'yes', how effective was it?

_____

21. Did you experience any detrimental effects from CAM?

Yes / No / difficult to judge

22. If 'yes', how detrimental was it?

_____

23. What was the cost to you? Please indicate the mean expenditure per month.

_____ Yen

24. Did your doctor or other medical professionals ask about CAM use?

Yes / No

25. Have you mentioned CAM use to your doctor?

Yes / No

26. If 'yes', how did your doctor respond?

1) encouraged you to continue using, 2) advised you to stop using,

3) was neutral about using (neither encouraged nor discouraged),

4) other ( )

27. If 'no', why did you not mention it to your doctor?

1) Because my doctor never asked me about the topic, 2) Because I thought my doctor would not understand, 3) Because I thought my doctor would disapprove of CAM use, 4) other ( )

28. Please answer the next question, if you have received or are receiving chemotherapy.

Have you ever used CAM products and anticancer drugs at the same time? CAM products include Chinese herbs, mushrooms, shark cartilage, etc. which are sold over the counter.

Yes / No

Thank you very much for your cooperation.

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ORIGINAL ARTICLE

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A phase I study of doxifluridine combined with weekly paclitaxel for metastatic gastric cancer

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Abstract *Purpose*: Based on the synergistic effect in preclinical studies, a phase I clinical trial for the combination of paclitaxel and doxifluridine (an intermetabolite of capecitabine) was performed to determine the recommended dose for the treatment of patients with metastatic gastric cancer. *Methods*: The dose of paclitaxel was increased from 60 mg/m^2 at level 1 to 90 mg/m^2 at level 5. It was administered as a 1-h infusion on days 1 and 8. The dose of doxifluridine was fixed at 600 mg/m^2 per day up to level 3, and escalated to 800 mg/m^2 per day at levels 4 and 5. It was administered orally for 2 weeks. The treatment was repeated every 3 weeks. *Results*: A total of 28 patients were enrolled. No dose-limiting toxicity (DLT) was observed at levels 1 and 2 (paclitaxel 70 mg/m^2). A DLT of grade 4 neutropenia lasting for more than 4 days was observed in one patient at level 3 (paclitaxel 80 mg/m^2). In addition, the first five of six patients in this group experienced grade 3 neutropenia during the first treatment cycle. A further six patients were added in order to confirm the safety of this dosage level, and no more DLTs except for grade 3 nausea in one patient were observed in the second cohort. No DLT was seen in three patients at level 4 (paclitaxel 80 mg/m^2). DLTs (grade 3 neuropathy in one patient and a treatment delay of the second cycle for more than 1 week due to grade 3 neutropenia in another) were observed in two out of six patients at level 5 (paclitaxel 90 mg/m^2), and this dose level was determined as the maximum tolerated dose. The tumor response rate was 42% (95% confidence interval 20–67%) in 19 patients with measurable lesions. *Conclusions*: The recommended dose was determined as 80 mg/m^2 of paclitaxel (days 1 and 8) and 800 mg/m^2 of doxifluridine (days 1–14) every 3 weeks. The results of this phase I study are encouraging and a phase II trial is thus warranted.

Keywords Doxifluridine · Thymidine phosphorylase · Taxane · Gastric cancer · Clinical trial

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Introduction

The incidence of gastric carcinoma is still high in Asia and it remains one of the leading causes of death [13, 28]. The prognosis for patients with unresectable or metastatic gastric carcinoma is poor, but chemotherapy confers a benefit when compared with best supportive care alone [9, 23]. In the past over 20 years, several anticancer drugs such as 5-fluorouracil (5-FU), cisplatin, methotrexate, doxorubicin, epirubicin, mitomycin, and etoposide, have been studied either alone or in combination as treatments for this disease. However, no new combination has yet emerged that is superior to 5-FU alone or to 5-FU plus cisplatin in terms of overall survival [13, 22, 31]. There is a pressing need for the evaluation of new agents such as the oral fluoropyrimidines and taxanes.

Paclitaxel promotes microtubule assembly and then exhibits its antitumor effect by arresting the cell cycle in the G_2/M phase. This mechanism of action is different from conventional anticancer drugs, and it has therefore been suggested that combination therapy with other anticancer drugs may be clinically effective [17]. The efficacy of paclitaxel has previously been confirmed clinically in various tumors including gastric cancer [1, 5, 10, 18, 19, 21, 33]. Furthermore, some promising regimens of paclitaxel combined with 5-FU/leucovorin/cisplatin, or with 5-FU/cisplatin have been reported in advanced gastric cancer [11, 14].

Preclinical studies have shown that paclitaxel induces thymidine phosphorylase (dThdPase) specifically in various human tumor tissues [26]. The oral fluoropyrimidine capecitabine and its intermetabolite doxifluridine are prodrugs that are converted to 5-FU by dThdPase in tumor tissues [6, 12]. A synergistic effect on inhibition of tumor growth has been reported when these agents are combined with paclitaxel [26]. Modest activity of capecitabine and doxifluridine has been reported in the treatment of advanced gastric cancer [7, 15, 20, 32]. Doxifluridine was approved for use in the treatment of advanced gastric cancer in 1987 in Japan, but capecitabine is still under investigation for this disease.

Thus, we conducted a phase I clinical trial in order to study the feasibility of paclitaxel/doxifluridine combined therapy. The tumor response was also investigated.

Patients and methods

Patients

All patients had to fulfill the following eligibility criteria: (1) histological confirmation of gastric adenocarcinoma; (2) inoperable metastatic disease or recurrent metastatic disease after surgery; (3) measurable or evaluable lesions; (4) aged from 20 to 75 years; (5) performance status (PS) ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) scale; (6) a maximum of one prior chemotherapy other than paclitaxel or doxifluridine for advanced disease (prior chemotherapy for advanced disease must have been completed at least 4 weeks prior to enrollment); (7) adequate bone marrow function (absolute granulocyte count $\geq 1500/mm^3$ and platelet count $\geq 100{,}000/mm^3$; (8) adequate liver function (serum bilirubin < 1.5 mg/dl and serum transaminase < 100 U/l); (9) adequate renal function (serum creatinine < 1.2 mg/dl); (10) no other severe medical conditions; (11) no other active malignancies; (12) no pregnant or lactating patients; (13) no peripheral neuropathy; and (14) provision of written informed consent.

This study was approved by the Institutional Review Board of the National Shikoku Cancer Center.

Dose-limiting toxicity and maximum tolerated dose

Dose-limiting toxicities (DLTs) were determined during the first treatment cycle. The definitions of DLTs were as follows: (1) grade 4 neutropenia lasting for at least 4 days, or grade 3 or 4 neutropenia with fever, (2) grade 4 thrombocytopenia, (3) grade 3 non-hematological toxicity, and (4) treatment delay of more than 2 weeks following the last administration of doxifluridine. The maximum tolerated dose (MTD) was defined as the dose level at which two of the three to six treated patients experienced DLT, and the recommended dose (RD) was determined at one level below.

Baseline evaluation included a complete medical history, physical examination, complete blood cell count, serum chemistry, urinary analysis, ECG, gastroscopy, gastrography, abdominal CT scan, and chest radiography. Blood, chemistry, urinary analyses, and subjective/objective symptoms for toxicity were monitored on a weekly basis during the treatment. Blood cell counts were determined at least every 2 days if hematological toxicities of grade 3 or more were seen in the first treatment cycle. When patients received the subsequent treatment cycle, they had to fulfill the previous eligibility criteria (7), (8), and (9), and their non-hematological toxicities had to recover to grade 1.

Toxicities were evaluated according to the National Cancer Institute common toxicity criteria (version 2.0).

Dosage and administration

The previous reports of phase I clinical trials studying the weekly administration of paclitaxel as a single agent in breast and ovarian cancer revealed that the RD was 80–100 mg/m^2 [16, 27]. We set the starting dose of paclitaxel (Taxol; Bristol-Myers Squibb Company, Tokyo, Japan) at 60 mg/m^2 and the dose was escalated by 10 mg/m^2 for each dose level up to dose level 3. Paclitaxel dissolved in 500 ml of an isotonic sodium chloride solution was administered on days 1 and 8 as an intravenous (i.v.) drip injection over 60 min following the short premedication (dexamethasone sodium phosphate 20 mg i.v. drip, diphenhydramine hydrochloride 50 mg orally, and ranitidine hydrochloride 50 mg i.v. 30 min before paclitaxel administration). Because 600–800 mg/m^2 per day of doxifluridine (Fulturon; Chugai Pharmaceutical Company, Tokyo, Japan) was considered the dose for patients with gastric cancer and this dose had been approved as the single-agent RD in Japan [20, 33], we fixed doxifluridine at the dose of 600 mg/m^2 per day and administered it orally at regular intervals four times a day (after each meal and before sleep) for 14 days. If the MTD did not reach level 3, the dose of each drug in the subsequent level was escalated in tandem by 10 mg/m^2 of paclitaxel and by 200 mg/m^2 of doxifluridine as shown in Table 1.

This treatment was repeated every 3 weeks (one cycle each) until disease progression or unacceptable toxicity was seen. The first cycle of the treatment was performed in the in-patient setting in our center. If the patient experienced DLT followed by no disease progression, the subsequent cycle was started at the next lower level after complete recovery from the toxic effects of the previous cycle.

Tumor response

Tumor response was evaluated every 6 weeks by means of CT scan. Measurable lesions were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [30].

Table 1 Dose level, number of patients enrolled, and DLT

Level	Paclitaxel (mg/m^2)	Doxifluridine (mg/m^2)	No. of patients	DLT
1	60	600	4	None
2	70	600	3	None
3	80	600	12	One grade 4 neutropenia lasting more than 4 days; one grade 3 nausea
4	80	800	3	None
5	90	800	6	One grade 3 neuropathy; one treatment delay due to neutropenia

Results

A total of 28 patients were enrolled, with 4 patients dosed at level 1, 3 at level 2, 12 at level 3, 3 at level 4, and 6 at level 5 from September 2001 to January 2003 (Table 1). Because one patient dosed at level 1 developed a grade 1 hypersensitivity reaction during the first treatment cycle and refused further treatment, a replacement patient was added to this dosage group. The patient characteristics are shown in Table 2. Of the 28 patients, 21 exhibited a good PS (0 or 1), and 22 had had a prior chemotherapy. The most frequent prior chemotherapy was 5-FU (17 patients). Nine patients had differentiated histological gastric adenocarcinoma, and the remainder had the undifferentiated type. The major metastatic sites were peritoneum, lymph nodes and liver.

The adverse events in the first cycle are summarized in Table 3. The most frequently observed toxicity was neutropenia. DLTs were not observed at levels 1 and 2, but a DLT (grade 4 neutropenia which continued for more than 4 days) was observed in the second patient at level 3. Then three patients were added to this dosage group. No DLT was observed in these additional patients. However, grade 3 neutropenia was observed in five patients (83%) in the first treatment cycle at this dose level. In addition, a 1-week postponement of the second cycle was needed due to the neutropenia in one patient and grade 4 neutropenia developed in another patient in the second cycle. Therefore, an additional six patients were enrolled in order to confirm the safety of this dose level. No DLT except for grade 3 nausea in one patient was observed in this second cohort, and we moved to the next dosage level. At level 4, grade 3 neutropenia was observed in two of three patients. However, no DLT was seen in this cohort. DLT (more than a 1-week treatment delay due to grade 3 neutropenia) was observed in the third patient at level 5. Three patients were added to this level. DLT (grade 3 peripheral neuropathy) was observed in the sixth patient. Grade 2 neuropathy appeared following the first administration of paclitaxel on day 1 and increased to grade 3 immediately after the second administration on day 8. The treatment was continued up to three cycles at the next lower dosage level, although grade 1 or 2 peripheral neuropathy developed during every cycle. From these results, level 5 was determined as the MTD and level 4 (paclitaxel 80 mg/m^2, doxifluridine 800 mg/m^2) was set as the RD. The lowest neutrophil counts in the first cycle at each dosage level are shown in Table 4. The medians of the lowest absolute neutrophil counts were graded as grade 3 neutropenia in levels 3, 4 and 5. Their values were apparently lower than those in levels 1 and 2. The period of recovery to grade 1 was around a week in levels 3, 4, and 5. It was also longer than that in levels 1 and 2.

The main toxicity of this combined therapy was myelotoxicity, neutropenia in particular. Grade 3 or 4 neutropenia was observed in 0 of 12 cycles (0%) at level 1, 1 of 20 cycles (5%) at level 2, 14 of 76 cycles (18%) at level 3, 3 of 13 cycles (23%) at level 4, and 3 of 15 cycles (20%) at level 5. Non-hematological toxicities of greater than grade 3 were observed in four patients during all treatment cycles. Two of these were the DLT. One of the remaining two patients showed grade 3 diarrhea in the fourth cycle at level 4, and the other patient showed grade 3 peripheral neuropathy after five cycles at level 5. A total of seven patients needed dose reduction during all treatment cycles. Four patients with DLT (Table 1) and two patients with grade 3 diarrhea and grade 3 peripheral neuropathy, respectively, were included. The other was the patient who showed grade 4 neutropenia in the second cycle at level 3. Peripheral neuropathy of grade 1 or 2 occurred in 2 of 12 patients at level 3, 1 of 3 patients at level 4, and 3 of 6 patients at level 5. It tended to be more severe following repeated administration of paclitaxel and seemed cumulative. Hand-foot syndrome

Table 2 Characteristics of patients

Age (years)	
Median	63
Range	44–75
Sex	
Male/female	16/12
Performance status (ECOG)	
0/1/2	10/11/7
Prior therapy	
Gastrectomy	20
Chemotherapy (5-FU)	22 (17)
Histological type	
Differentiated	9
Undifferentiated	19
Sites of metastasis	
Liver	6
Abdominal lymph nodes	17
Lung	5
Peritoneum	19
Spleen	2

Table 3 Adverse reactions during the first treatment cycle

Toxicity	Level 1 ($n=4$)		Level 2 ($n=3$)		Level 3 ($n=6$)				Level 4 ($n=3$)		Level 5 ($n=6$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematological												
Leukopenia	2	0	2	1	5	1	1	2	2	0	5	0
Neutropenia	3	0	2	1	1	5[a]	3	2	0	3	3	2[a]
Lymphocytopenia	4	0	1	1	1	0	1	1	2	0	6	0
Anemia	3	1	3	0	4	1	5	0	0	2	4	1
Thrombocytopenia	2	0	0	0	0	0	2	0	0	0	1	0
Non-hematological												
Hypersensitivity reaction	1	0	0	0	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	2	0	0	0	1	0	1	0	3	0	0	0
Nausea	2	0	0	0	0	0	1	1[a]	0	0	2	0
Vomiting	0	0	0	0	0	0	1	0	0	0	0	0
Anorexia	1	0	0	0	1	0	0	0	2	0	1	0
Diarrhea	0	0	0	0	2	0	1	0	2	0	0	0
Stomatitis	1	0	0	0	0	0	0	0	0	0	1	0
Alopecia	1	–	0	–	3	–	2	–	2	–	5	–
Edema	0	0	0	0	0	0	0	0	0	0	0	0
Hand-foot syndrome	0	0	0	0	0	0	0	0	0	0	0	0
Rash	1	0	0	0	0	0	1	0	0	0	0	0
Palpitations	0	0	0	0	0	0	1	0	1	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	0	0	1	0	0	1[a]

[a]DLT was observed in one patient