these results, the dosage schedule at level 3 or 4 seems to be highly feasible.

Conventional 3-h infusion of paclitaxel with a 3-week interval combined with infusional 5-FU and cisplatin was studied in Korean group in a phase II trial in advanced gastric cancer [14]. A high response rate of 51% and good tolerability was reported in this study. Recently, it has been reported from Germany that weekly administration of paclitaxel with a combination of 5-FU/folinic acid and cisplatin showed a reduced incidence of hematological toxicity, particularly leukopenia, and other toxicities, apart from a slightly higher incidence of peripheral neuropathy, were also comparable between the weekly regimen and the conventional regimen [11]. The response rate (50%) in this German phase II study in advanced gastric cancer was well maintained with the weekly regimen.

Active oral fluoropyrimidines, such as capecitabine, S-1, and uracil/ftorafur (UFT) plus leucovorin have recently been developed [3, 15, 25]. Based on promising reports, trials are being urgently undertaken in many countries to determine whether 5-FU combined with various agents could be replaced by these new oral fluoropyrimidines. Although most patients in our study had received prior chemotherapy, this doxifluridine and paclitaxel combined therapy yielded a high response rate of 42% (95% confidence interval 20–67%). In addition, elimination of ascites was observed in two of three patients. The efficacy of this combination therapy would also be expected in patients with peritoneal dissemination that is frequently seen in advanced gastric cancer. These results encouraged us to move to further trials.

In conclusion, we performed a phase I clinical trial using a combination of paclitaxel and doxifluridine, and determined the RD as 80 mg/m^2 of paclitaxel on days 1 and 8, and 800 mg/m^2 per day of doxifluridine for 2 weeks in a 3-week treatment schedule. The results of our present study are promising and a phase II clinical trial of this combination therapy is planned in which the safety of the RD will be investigated carefully in the first six or more patients.

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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

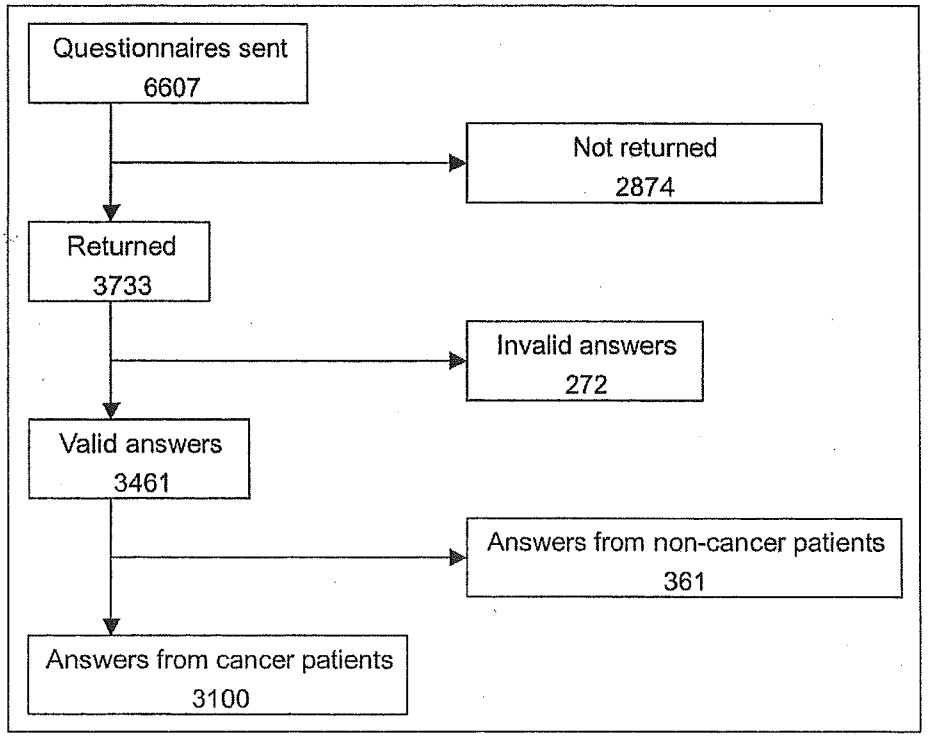

Fig 1. Flow diagram of the study population.

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	968	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	666	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)	1.39	1.18 to 1.64	< .0001	1.32	1.08 to 1.61	.0063
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

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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*.

1. _____ 2. _____

3. _____ 4. _____

5. _____ 6. _____

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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Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies

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Background: To explore the association between hydration volume and symptoms during the last 3 weeks of life in terminally ill cancer patients.

Patients and methods: This was a multicenter, prospective, observational study of 226 consecutive terminally ill patients with abdominal malignancies. Primary responsible physicians and nurses evaluated the severity of membranous dehydration (dehydration score calculated from three physical findings), peripheral edema (edema score calculated from seven physical findings), ascites and pleural effusion (rated as physically undetectable to symptomatic), bronchial secretion, hyperactive delirium (Memorial Delirium Assessment Scale), communication capacity (Communication Capacity Scale), agitation (Agitation Distress Scale), myoclonus and bedsores.

Results: Patients were classified into two groups: the hydration group ($n=59$) who received 1 l or more of artificial hydration per day, 1 and 3 weeks before death, and the non-hydration group ($n=167$). The percentage of patients with deterioration in dehydration score in the final 3 weeks was significantly higher in the non-hydration group than the hydration group (35% versus 14%; $P=0.002$), while the percentages of patients whose symptom scores for edema, ascites and pleural effusion increased were significantly higher in the hydration group than the non-hydration group (44% versus 29%, $P=0.039$; 29% versus 8.4%, $P<0.001$; 15% versus 5.4%, $P=0.016$; respectively). After controlling for multiple covariates and treatment settings, the association between hydration group and dehydration/ascites score was statistically significant. Subgroup analysis of patients with peritoneal metastases identified statistically significant interaction between hydration group and dehydration/pleural effusion score. There were no significant differences in the degree of bronchial secretion, hyperactive delirium, communication capacity, agitation, myoclonus or bedsores.

Conclusions: Artificial hydration therapy could alleviate membranous dehydration signs, but could worsen peripheral edema, ascites and pleural effusions. It is suggested that the potential benefits of artificial hydration therapy should be balanced with the risk of worsening fluid retention symptoms. Further clinical studies are strongly needed to identify the effects of artificial hydration therapy on overall patient well-being, and an individualized treatment and close monitoring of dehydration and fluid retention symptoms is strongly recommended.

Key words: dehydration, neoplasm, palliative care, rehydration, water depletion

Introduction

The dehydration–rehydration problem has been one of the most important issues in palliative or end-of-life care literature over the two last decades [1]. Current discrepancies in the practice of artificial hydration therapy for terminally ill cancer patients have the potential to cause serious clinical problems: patients could suffer from unnecessary dehydration-related

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symptoms or experience iatrogenic over-hydration symptoms [2–5]. These discrepancies are largely due to the lack of evidence about the effects of artificial hydration therapy on patient well-being [3].

Traditionally, artificial hydration therapy has been thought not to benefit the terminally ill [6–11]; however, some recent studies have demonstrated that appropriate hydration can contribute to patient comfort [12–16]. The majority of studies on this topic are limited by methodological issues [17], and do not provide enough of a basis for the evidence-based practice of artificial hydration therapy in terminally ill patients. The aim of the present study was to explore systematically the associations between hydration volume and dehydration and fluid retention symptoms in the last 3 weeks of life in terminally ill patients with abdominal malignancies.

Patients and methods

Patients

The study subjects were consecutive terminally ill cancer patients treated in 14 oncology units, 19 palliative care units and four home-based palliative care programs in Japan. The participating institutions recruited potential participants following the same inclusion criteria: age >20 years; life expectancy estimated by a physician to be ≤3 months; and incurable malignancy of abdominal origin (excluding hepatic malignancies). Exclusion criteria were: liver cirrhosis of any etiology, renal failure, nephrotic syndrome, protein-losing enteropathy, intra-abdominal shunt for ascites, hypercalcemia, adrenalopathy, thyroid diseases, and other complications of the circulatory, respiratory, hepatic, or renal system unrelated to underlying malignancies; surgical, radiological or oncological treatments with the primary intent of tumor reduction in the 3 weeks prior to study inclusion; existing communication difficulty such as aphasia or aphonia; and the use of artificial enteral nutrition. Patients were enrolled from August 2002 to February 2003, and followed until March 2003.

Study design

This was a multicenter, prospective, observational study. From the time of study inclusion, primary responsible physicians prospectively recorded patients' dehydration and fluid retention symptoms on a structured data-collecting sheet every week as a part of daily practice. In addition, symptoms observed very close to death were assessed after patients died, because it was impossible to predict when the patients would die, and because assessments on a daily basis would present a high burden for patients and physicians. Thus, within 72 h after patient death, patients' dehydration and fluid retention symptoms 24 h before death, communication capacity during the 3 days before death and degree of agitation in the week before death were recorded. To minimize the recall bias, the evaluations were based on the full agreement of the primary physicians and primary nurses.

The patients received the usual treatments from their institutions. The indications for hydration therapy, administration methods and modification of treatment regimen over time were dependent on each physician's clinical decisions. We did not standardize hydration treatments, because patients' and families' wishes and each physician's philosophy strongly influenced actual hydration practice [3], and adopting a single hydration protocol was regarded as inappropriate outside experimental study designs. Instead, we described the details of hydration treatments actually performed for interpretation of the results.

This study was approved by the Institutional Review Board of each hospital, and conducted in accordance with the Declaration of Helsinki.

End points and measurements

The primary end points of this study were dehydration and fluid retention symptoms in the last 3 weeks of life. Although patient-reported symptoms and satisfaction are important outcomes in palliative care [18], we chose symptoms that could be objectively evaluated as the end points for this study. The rationale for this decision was that adopting self-report measures could result in higher rates of patient exclusion and unacceptable selection bias, because patient reports are often impossible in the very late stages of cancer due to cognitive impairment, and because symptom evaluations based on patient self-reports are not routinely used in many participating institutions [19, 20].

Physical symptoms

Physicians were requested to perform physical examinations in the morning at least 1 h after patients had eaten. The degree of dehydration was assessed on the basis of three physical findings: moisture on the mucous membranes of the mouth (0, moist; 1, somewhat dry; 2, dry), axillary moisture (0, moist; 1, dry) and sunkenness of eyes (0, normal; 1, slightly sunken; 2, sunken). These signs were selected due to their significant correlations with biological dehydration, as previously confirmed in elderly patients [21–23]. Empirical studies have found that the sensitivity/specificity of each sign in identifying dehydration is 85%/58%, 50%/82% and 62%/82%, respectively [21–23]. *Ad hoc* dehydration score (range 0–5) was calculated as the total of these three scores. A higher score thus indicated a higher level of dehydration.

The severity of peripheral edema was determined through the examination of seven regions: the hands, forearms, upper arms, feet, lower legs, thighs and trunk. Peripheral edema severity was scored based on the degree of increased skin thickness in the middle of each region (0, none; 1, mild, thickness of <5 mm; 2, moderate, 5–10 mm; 3, severe, >10 mm). If peripheral edema was asymmetric, the more severe side was rated unless the asymmetry was caused by a unilateral vascular obstruction; in these cases, the non-obstructed side was rated. The peripheral edema score (range 0–21) was calculated as the total of the severity scores for the seven regions. A higher score indicated more severe edema.

Pleural effusion and ascites were each rated on a scale of 0 to 2 (0, physically non-detectable; 1, physically detectable but asymptomatic; 2, symptomatic or tense ascites). Myoclonus and bedsores were considered present when they were observed at any time in the final 3 weeks of life.

Bronchial secretion was defined as sounds audible at the bedside produced by movement of secretions in the hypopharynx or the bronchial tree in association with respiration [8]. The severity of bronchial secretion was evaluated using a previously proposed scale: 'inaudible' (score 0), 'audible only very close to the patient' (score 1), 'clearly audible at the end of the bed in a quiet room' (score 2) and 'clearly audible at about 6 m or at the door of the room' (score 3) [24]. Bronchial secretions were considered present when patients had a severity score of 1 or more, received any anti-muscarinic medications to reduce bronchial secretion or received oral/bronchial suctioning at least once during the final 3 weeks of life. Severe bronchial secretion was defined as severity score of 2 or 3 at any time during the final 3 weeks.

Psychiatric symptoms

We used selected items of the Communication Capacity Scale, the Agitation Distress Scale and the Memorial Delirium Assessment Scale to evaluate psychiatric symptoms [25, 26]. The Communication Capacity Scale is a validated five-item observer-rating scale used to quantify communication

capacity in terminally ill patients [25]. The Agitation Distress Scale is a six-item observer-rating scale used to quantify the levels of agitation in delirious terminal patients [25]. Although using all items of a scale is psychometrically ideal, we used select items in order to reduce physician burden and increase patient enrollment [27].

The patients' communication capacity was assessed using the highest scores measured in the last 3 days of life on three items: the 'reduced level of consciousness' item of the Memorial Delirium Assessment Scale, and the 'answers to closed-ended questions' and 'voluntary communication' items from the Communication Capacity Scale. Communication score (range 0–9) was calculated as the total of these three items, such that a higher score indicated a greater capacity for communication (Cronbach's α coefficient = 0.94). The correlations between total score on this abbreviated scale and the total score on the Communication Capacity Scale was high in the original validation data (Spearman's $\rho = 0.94$; $P < 0.001$) [25].

The degree of agitation was defined as the most severe symptoms experienced during the last week of life, and quantified using four items from the Agitation Distress Scale: the frequency of motor anxiety, extent of motor anxiety, contents of motor anxiety and psychological instability. The agitation score (range 0–12) was calculated as the total of these four items; a higher score indicated higher levels of agitation (Cronbach's α coefficient = 0.87). The correlations between total score on this abbreviated scale and the total score on the Agitation Distress Scale was high in the original validation data (Spearman's $\rho = 0.95$; $P < 0.001$) [25].

Hyperactive delirium was assessed using the 'psychomotor activity' item of the Memorial Delirium Assessment Scale, which grades increased psychomotor activity on a scale of 0 (normal) to 3 (severe) [26]. Hyperactive delirium was defined as a score of 2 or 3 on this scale.

Covariates of main outcomes

We recorded the presence or absence of the following potential covariates: stomatitis, oxygen requirement, and use of opioids, diuretics and anticholinergic medication (dehydration score); vascular obstruction, and use of non-steroidal anti-inflammatory drugs (NSAIDs), steroids and diuretics (edema score); peritoneal and liver metastasis (ascites); lung and pleural metastasis, and pneumonia (pleural effusion); and intestinal obstruction and oral intake of fluids (for all symptoms) [6, 8, 15, 28].

Statistical analyses

We analyzed data for patients who died at least 3 weeks after their initial evaluation. The rationale for this decision was that we had no appropriate instruments to indicate reliable base-line points for analyses, and hydration therapy was likely to influence patient symptoms after a considerable time lag (i.e. hydration volume the patients had received 1–3 weeks before death could affect patients symptoms 48 h before death). To examine a bias, we compared patient backgrounds between the excluded and included patients.

We divided patients into two groups: those who received artificial hydration of 1 l/day or more both 1 week and 3 weeks before death (hydration group: total $n = 59$; 31 from oncology and 28 from palliative/home-care settings) and those who did not (non-hydration group: total $n = 167$ [18], from oncology and 149 from palliative/home-care settings). This classification was determined on the basis of actual data distributions, and the results using the other classifications achieved the similar conclusions.

To explore the potential association between hydration groups and patient symptoms, we compared the number of patients whose symptom scores increased in the final 3 weeks (dehydration and edema scores by three or more points; ascites and pleural effusion scores by one or more point) between the hydration and non-hydration groups. The results using the other cut-off points achieved the same conclusions. We also compared the prevalence of bronchial secretion, hyperactive delirium, myoclonus and bedsores, the degree of communication capacity, and the degree of agitation between the two groups.

To explore the effects of covariate factors and treatment settings, we examined the potential interactions between hydration groups and changes in dehydration score, edema score, and ascites and pleural effusion severity scores by the repeated measurement analysis with the covariates entered into the models (robust variance with the Proc mixed procedure). No covariates except for peritoneal metastasis and treatment settings statistically influenced the outcomes. In addition, subgroup analyses for patients who drank <500 ml/day of fluids throughout the last 3 weeks of life ($n = 108$), patients with intestinal obstruction ($n = 114$) and patients who received no intestinal drainage ($n = 192$) achieved the same results. We therefore reported the results for the entire sample with adjusted P values to allow for difference in peritoneal metastasis and treatment settings, as well as subgroup analysis of patients with peritoneal metastases ($n = 145$).

Finally, to provide additional information for interpreting data, we compared the changes in blood urea nitrogen/creatinine levels between hydration and non-hydration groups using repeated measurement analysis. We also calculated the prevalence of fluid retention symptoms 24 h before death among dehydrated patients, defined as presence of dry axillary (diagnosis on the basis of sunken eyes achieved similar results).

Univariate analyses were conducted using the χ^2-test (Fisher's exact method) and the Mann–Whitney U-test, where appropriate. All analyses were performed using the statistical package SAS.

Results

Patient background

All 498 patients who met the inclusion criteria were consecutively recruited for this study, but a total of 272 patients were excluded for the following reasons: death within 3 weeks of initial assessment ($n = 200$), survival beyond the observation period ($n = 35$), medical complications ($n = 17$), prior communication difficulty ($n = 15$) and discharge ($n = 5$). Thus, a total of 226 patients (49 from oncology units and 177 from palliative/home-care settings) were finally analyzed. There were no statistically significant differences in patient age and primary tumor sites between the patients excluded from the study due to death within 3 weeks and those analyzed, but the former was more likely to be male (Table 1).

Patient backgrounds are summarized in Table 2. There were significant differences in primary tumor sites, prevalence of lung and peritoneal metastases, vascular obstruction, intestinal obstruction, the use of NSAIDs and steroids, and oral intake 3 weeks and 1 week before death between the hydration and non-hydration groups. Chemotherapy was performed in seven patients.

Table 3 summarizes hydration practice in the study subjects. The mean hydration volume in the hydration group ranged from 838 to 1405 ml/day during the last 3 weeks, and the median hydration volume in the non-hydration group was 200 ml/day at all three observation points.

At baseline, ascites was present but asymptomatic in 27% ($n = 62$) and symptomatic in 20% ($n = 44$) of all patients.

Table 1. Characteristics of excluded and included patients

	Excluded patients[a] ($n=200$)	Included patients ($n=226$)	P
Age, years (mean ± SD)	67 ± 12	68 ± 12	0.63
Gender			
Male	114	106	0.037
Female	86	120	
Primary site			
Stomach	76	74	0.25
Colon	35	47	
Pancreas	36	35	
Rectum	15	31	
Bile duct	15	12	
Ovary	5	10	
Others	18	17	

[a]Patients who died within 3 weeks of initial assessment.
SD, standard deviation.

Pleural effusion was present but asymptomatic in 12% ($n=27$) and symptomatic in 6.6% ($n=15$) of all patients.

Dehydration

The percentage of patients whose dehydration score increased by three or more points in the final 3 weeks of life was significantly higher in the non-hydration group than in the hydration group [35% ($n=59$) versus 14% ($n=8$); $P=0.0020$]. After controlling for covariates and treatment settings, there was a statistically significant interaction between hydration group and changes in the dehydration score (1.6 ± 1.4 3 weeks before death to 2.7 ± 1.6 24 h before death in the hydration group versus 1.3 ± 1.3 to 3.2 ± 1.5 in the non-hydration group; $P=0.0043$) (Figure 1).

Edema

The number of patients whose edema scores increased by three or more points was significantly higher in the hydration group than in the non-hydration group [44% ($n=26$) versus 29% ($n=49$); $P=0.039$]. After controlling for covariates and treatment settings, the interaction between hydration group and changes in the edema score did not reach statistical significance (2.2 ± 3.3 3 weeks before death to 6.1 ± 6.4 24 h before death in the hydration group versus 3.5 ± 4.5 to 5.2 ± 5.2 in the non-hydration group; $P=0.15$) (Figure 1).

Ascites

The percentage of patients whose symptom score increased by one or more point during the final 3 weeks was significantly higher in the hydration group than in the non-hydration group [29% ($n=17$) versus 8.4% ($n=14$); $P<0.001$]. After controlling for covariates and treatment settings, there was a statistically significant interaction between hydration group and changes in the ascites score (0.73 ± 0.78 3 weeks before death to 0.92 ± 0.88 24 h before death in the hydration group versus 0.64 ± 0.79 to 0.58 ± 0.74 in the non-hydration group; $P=0.035$) (Figure 1).

Table 2. Patient characteristics

Characteristic	Hydration group ($n=59$) [% (n)]	Non-hydration group ($n=167$) [% (n)]	P
Age, years (mean ± SD)	67 ± 13	68 ± 11	0.36
Gender			
Male	58 (34)	43 (72)	0.055
Female	42 (25)	57 (95)	
Primary site			
Stomach	49 (29)	27 (45)	0.008
Colon	20 (12)	21 (35)	
Pancreas	19 (11)	14 (24)	
Rectum	5.1 (3)	17 (28)	
Bile duct	3.4 (2)	6.0 (10)	
Ovary	0	6.0 (10)	
Others	3.4 (2)	9.0 (15)	
Metastatic sites			
Lung	12 (7)	30 (50)	0.006
Pleura	15 (9)	15 (25)	0.96
Liver	46 (27)	44 (73)	0.79
Peritoneum	78 (46)	59 (99)	0.010
Performance status at enrolment			
≥2	29 (17)	19 (31)	0.59
3	37 (22)	42 (70)	
4	34 (20)	40 (66)	
Medical complications			
Stomatitis	12 (7)	23 (39)	0.060
Vascular obstruction of both extremities	1.7 (1)	12 (20)	0.018
Intestinal obstruction	64 (38)	46 (76)	0.013
Pneumonia	15 (9)	16 (27)	0.87
Medical treatments			
Oxygen	69 (41)	55 (92)	0.053
NSAIDs	53 (31)	71 (119)	0.009
Opioids	81 (48)	84 (141)	0.58
Steroids	54 (32)	75 (126)	0.002
Diuretics	34 (20)	32 (53)	0.76
Anti-cholinergic medications	20 (12)	25 (42)	0.46
Oral intake fluids ≥500 ml/day			
3 weeks before death	80 (47)	42 (70)	<0.001
1 week before death	83 (49)	57 (96)	<0.001
24 h before death	86 (51)	84 (140)	0.63

SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3. Hydration practice in the final 3 weeks

	3 weeks before death [% (*n*)]	1 week before death [% (*n*)]	24 h before death [% (*n*)]
All patients			
<500 ml/day	44 (100)	48 (109)	62 (139)
500–1000 ml/day	21 (47)	22 (49)	21 (48)
≥1000 ml/day	35 (79)	30 (68)	17 (39)
Hydration group ($n=59$)			
Hydration volume, ml/day [mean ± SD (median)]	1405±479 (1300)	1253±379 (1100)	838±580 (1000)
Continuous administration	63 (37)	66 (39)	61 (36)
Intermittent administration	37 (22)	34 (20)	24 (14)
Via a central vein	76 (45)	75 (44)	61 (36)
Via a peripheral vein	24 (14)	25 (15)	22 (13)
Hyperalimentation	56 (33)	54 (32)	31 (18)

SD, standard deviation.

Pleural effusion and bronchial secretion

The number of the patients whose pleural effusion symptom score increased by one or more point in the final 3 weeks was significantly higher in the hydration group than in the non-hydration group [15% ($n=9$) versus 5.4% ($n=9$); $P=0.016$]. Hydration group was not significantly associated with changes in the pleural effusion symptom score after controlling for covariates and treatment settings (0.22±0.46 3 weeks before death to 0.36±0.61 24 h before death in the hydration group versus 0.27±0.60 to 0.31±0.63 in the non-hydration group; $P=0.76$) (Figure 1).

There was no statistically significant difference in the prevalence of bronchial secretion between the hydration and the non-hydration groups (Table 4).

Communication capacity, agitation and delirium

There were no statistically significant differences in the communication score, agitation score or prevalence of hyperactive

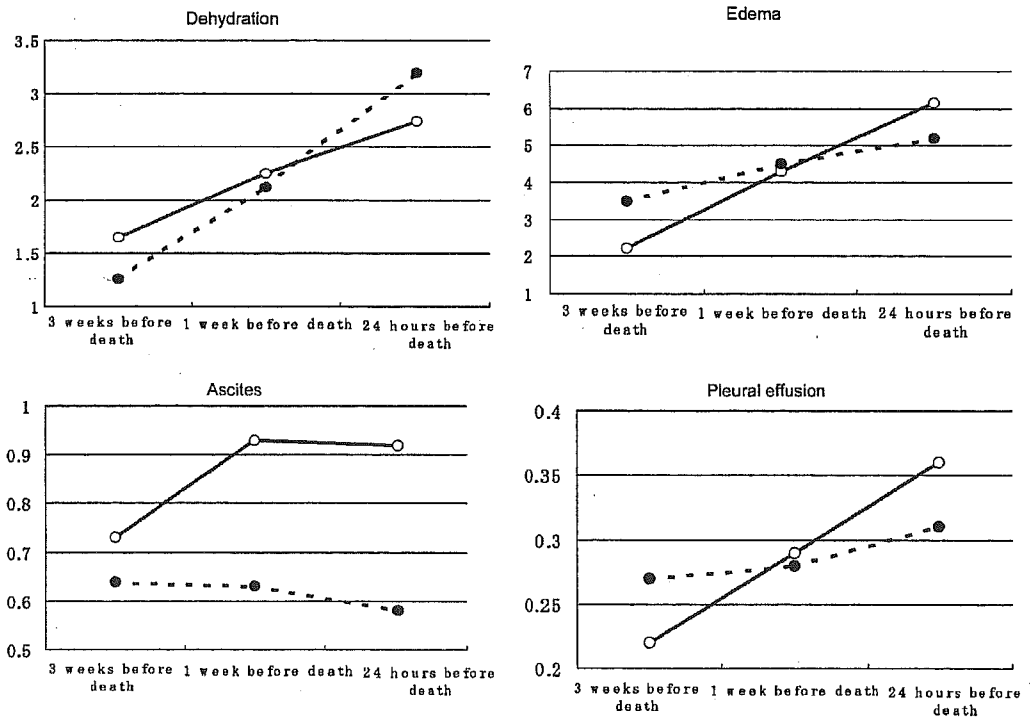

Figure 1. Effects of hydration on dehydration and fluid retention symptoms. Open circles, hydration group ($n=59$); filled circles, non-hydration group ($n=167$).

Table 4. Symptom severity in the last 3 weeks of the patients with and without hydration

	Hydration group ($n=59$)	Non-hydration group ($n=167$)	P
Bronchial secretion[a] [% (n)]	44 (26)	46 (77)	0.79
Severe bronchial secretion[b] [% (n)]	19 (11)	17 (28)	0.74
Communication score[c] (mean ± SD)	3.2 ± 3.0	3.7 ± 3.1	0.30
Agitation score[d] (mean ± SD)	2.1 ± 2.8	2.3 ± 2.7	0.35
Hyperactive delirium[e] [% (n)]	12 (7)	13 (22)	0.80

[a]Defined as audible bronchial secretion, requirement of any anti-muscarinic medications or oral/bronchial suctioning.
[b]Defined as clearly audible bronchial secretion.
[c]The total score of one item from the Memorial Delirium Assessment Scale and two items from the Communication Capacity Scale. Higher scores indicate higher levels of communication capacity.
[d]The total score of four items from the Agitation Distress Scale. Higher scores indicate higher levels of agitation.
[e]Defined as scores of 2 or 3 on the psychomotor activity item of the Memorial Delirium Assessment Scale.

delirium between the hydration and the non-hydration groups (Table 4).

Myoclonus and bedsores

There were no statistically significant differences in the prevalences of myoclonus or bedsores between the hydration and the non-hydration groups [for myoclonus 1.7% ($n=1$) versus 8.4% ($n=14$), $P=0.12$; for bedsores 27% ($n=16$) versus 34% ($n=57$), $P=0.32$].

Patients with peritoneal metastases

The interactions between hydration group and symptom changes in the last 3 weeks were statistically significant in dehydration score (1.7 ± 1.43 weeks before death to 2.9 ± 1.6 24 h before death in the hydration group versus 1.3 ± 1.3 to 3.5 ± 1.4 in the non-hydration group; $P=0.0043$) and pleural effusion score (0.22 ± 0.47 to 0.35 ± 0.60 versus 0.30 ± 0.63 to 0.27 ± 0.57, respectively; $P=0.046$), and marginally significant in ascites score (0.91 ± 0.78 to 1.0 ± 0.87 versus 0.88 ± 0.80 to 0.70 ± 0.75, respectively; $P=0.091$).

Table 5. Fluid retention symptoms in dehydrated patients ($n=149$)

	% (n)
Peripheral edema	
Hands and/or feet	69 (102)
Forearms and/or lower legs	56 (83)
Upper arms and/or thigh	36 (54)
Trunk	26 (39)
Any peripheral edema	73 (108)
Ascites	46 (69)
Pleural effusion	19 (29)
Any fluid retention symptoms	81 (121)

Dehydration was diagnosed as present if the axillary moisture was rated as dry 24 h before death.

Laboratory findings

We obtained paired blood samples taken 3 weeks and 1 week before death from 37 (63%) and 56 (34%) patients in the hydration and non-hydration groups, respectively. The blood urea nitrogen/creatinine levels increased from 34 ± 15 to 44 ± 18 mg/dl in the hydration group in the last 3 weeks, compared with from 31 ± 17 to 39 ± 20 mg/dl in the non-hydration group. The difference between hydration groups was not statistically significant ($P=0.58$).

Comorbidity of dehydration and fluid retention symptoms

Of the 149 dehydrated patients with dry axillary 24 h before death, 73%, 46% and 19% had simultaneous edema, ascites or pleural effusion, respectively; and 81% had some fluid retention symptoms (Table 5).

Discussion

This is, to the best of our knowledge, the largest and the first multicenter observation study to investigate the association between hydration volume and dehydration and fluid retention symptoms in terminally ill cancer patients.

This study revealed that peripheral edema, ascites and pleural effusion in the hydration group were more likely to worsen in the last 3 weeks. The association between hydration group and ascites severity was statistically significant after controlling all covariates and treatment settings, and in a subgroup of patients with peritoneal metastases there was a statistically significant interaction between hydration practice and changes in pleural effusion severity. The underlying mechanisms of fluid retention symptoms include a decrease in colloid osmotic pressure, an increase in membrane permeability, and an increase in hydrostatic pressure [11]. Our findings suggest that overhydration in the terminal phase could deteriorate fluid retention symptoms.

We also found that dehydration scores increased in the last 3 weeks of life regardless of whether patients received artificial hydration or not, although scores increased less in the hydration than in the non-hydration group. The potential interpretations of this finding are that: (i) the instruments for measurement of dehydration used in this study could not differentiate dehydration signs from changes related to progressed cachexia; (ii) current hydration volume was not sufficient to maintain hydration status and more active hydration could alleviate membrane dehydration signs; or (iii) artificial hydration therapy in the terminal stage could not effectively alleviate dehydration even if an appropriate volume was provided due to some pathological mechanisms (e.g. fluid shift from the intravascular components to the third space). The first

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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