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ORIGINAL REPORT

Complementary and Alternative Medicine Use by Patients Enrolled Onto Phase I Clinical Trials

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ABSTRACT

Purpose
To describe the prevalence, clinical characteristics, and pattern of use of complementary and alternative medicine (CAM) in patients enrolled onto phase I trials.

Patients and Methods
Questionnaires were administered to 108 patients with advanced malignancies enrolled onto phase I chemotherapy trials at the Mayo Clinic Comprehensive Cancer Center (Rochester, MN). CAM was classified into two modalities, pharmacologic and nonpharmacologic. Clinical and demographic data, including age, sex, and prior cancer treatment, were subsequently obtained from patient charts and examined for any correlation with CAM use, using χ^2 analysis.

Results
One hundred two survey forms were returned. Among respondents, 88.2% (90 of 102) had used at least one CAM modality; 93.3% (84 of 90) and 53.3% (48 of 90) had used pharmacologic and nonpharmacologic CAM, respectively; and 46.7% (42 of 90) used both modalities. Vitamin and mineral preparations constituted 89.3% (75 of 84) of all pharmacologic CAM used. Intake was highest for vitamins E (48.8% [41 of 84]) and C (38.1% [32 of 84]), and 71.4% (60 of 84) of respondents took nonvitamin/mineral agents. Green tea (29.8% [25 of 84]), echinacea (13.1% [11 of 84]), and essiac (9.5% [8 of 84]) were the most popular. Prayer and spiritual practices were the most commonly used nonpharmacologic CAM, accounting for 52.1% (25 of 48). Chiropractors, the most frequently visited nontraditional medicine practitioners, were consulted by only 10% (9 of 90) of those who practiced CAM. Both CAM modalities were used more frequently by women (53.5% [23 of 43]) than men (40.4% [19 of 47]).

Conclusion
CAM use is common among patients in phase I trials and should be ascertained by investigators, because some of the agents used may interact with investigational agents and affect adverse effects and/or efficacy.

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INTRODUCTION

Complementary and alternative medicine (CAM), as defined by the National Center for Complementary and Alternative Medicine, refers to "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine." CAM has gained not only widespread popularity in recent years among the general population, but increasing acceptance among clinicians as well. One recent study reported that 60% of unorthodox treatments were provided by physicians.[1] Numerous studies dealing with popular CAM drug therapies have been published in the last decade alone.[2-4] Other studies have dealt exclusively with vitamins and minerals.[5-9] The estimated prevalence of CAM use by cancer

patients ranged from 7% to 64% in a review of 26 surveys across 13 countries.[10] Differences were observed among patient groups (outpatient *v* inpatient, pediatric *v* adult, specific cancer groups) and different CAM treatments studied.[10] Richardson et al found that 83.3% of cancer patients surveyed had used at least one CAM modality.[11] There have been multiple reports published in recent years regarding CAM practice among adult patients with cancer. In most studies to date, CAM users tended to be female, younger (aged 30 to 50 years), and educated patients with higher incomes.[11-16] Most cancer patients combine, rather than replace, conventional therapy with CAM.[1,17,18] Moreover, CAM usage seemed to be more prevalent with advanced disease.[11,16]

Concurrent use of investigational agents and certain pharmacologic CAM agents can cause potentially harmful drug interactions.[19] Phase I pharmacology studies seek to determine clinically relevant dosing schema for new drugs or drug combinations by characterizing the safety profile and pharmacokinetics of the drugs under investigation. The pharmacokinetic properties, incidence of adverse effects, and the extent of antitumor activity of investigational drugs may thus be affected by the undocumented use of other pharmacologic agents, such as biologic CAM therapies. Information on the pattern of CAM use among patients in phase I trials is, therefore, critical.

Data on CAM use by patients in phase I trials are not available. As most patients in phase I cancer clinical trials have advanced metastatic disease, we hypothesized that the prevalence of CAM use in this group would be high given the association between disease stage and extent of CAM use. This study was thus conducted to estimate the prevalence and describe the distribution of CAM use among patients enrolled onto phase I trials at the Mayo Clinic Comprehensive Cancer Center (Rochester, MN) in order to provide medical professionals and scientists engaged in drug development studies with useful background information on patients' use of CAM.

PATIENTS AND METHODS

In 1999, the Mayo Clinic institutional review board approved a cross-sectional study, using a structured questionnaire-survey form in English, for patients 18 years or older participating in the various phase I chemotherapeutic protocols at the Mayo Clinic Comprehensive Cancer Center. Permission to contact each patient was requested from the primary oncologist. From 1999 to 2002, all eligible patients enrolled onto various phase I trials were approached by one registered nurse (L.J.H.), and verbal consent was obtained. Patients were assured that refusal to enroll in the study would not affect their present or future care in any way, and they were informed that they could skip any question. Patients answered the questionnaires in their leisure time and returned the forms by no later than their next clinical visit. The study was closed after the 102nd survey form was submitted. All questionnaires were numerically coded to ensure confidentiality of responses.

Questionnaire

We defined CAM in the framework of the definition adopted by the Cochrane collaboration.[20] The questionnaire, designed to be completed within 10 to 20 minutes, consisted of six sections: (1) CAM with known pharmacotherapeutic effects, such as vitamins, herbs, and other oral supplements (eg, echinacea); (2) special diets; (3) other nonpharmacologic therapies, such as psychotherapy, movement, or spiritual practices; (4) visits to CAM practitioners; (5) an open format section for patients' opinions on any other programs that were of subjective benefit, either physically or pyschologically; (6) patients' highest academic degree attained, and patients' cancer treatments received before enrollment in phase I trials. A detailed description of the pharmacologic and nonpharmacologic CAM modalities is given in Table 1. The first section of the questionnaire listed different CAM agents and how frequently they were used (everyday, at least 2× a week, sometimes, never). The subsequent sections gathered information on current use of nonpharmacologic types of CAM.

Analysis

CAM users were defined as those who reported using at least one form of CAM. Questions left unanswered on the questionnaire were treated as negative responses. Descriptive statistics, frequency distributions, and Spearman correlations were used to summarize the data and examine associations of CAM use (overall, pharmacologic, nonpharmacologic, or both) with patient demographics and prior cancer treatments.[21] In addition, summary proportions along with the 95% exact binomial CIs were calculated to quantify the prevalence of CAM use.[22]

RESULTS

Patient Characteristics

Of the 108 patients who consented to the survey, 102 returned the forms. Pertinent demographic and clinical data are shown in Table 2. The median age of the respondents was 59 years (range, 27 to 78 years). All patients except one were white (one was African American). There were 48 women (47%) and 54 men (53%). High school was the highest level of educational attained by 40.4% of respondents (40 of 99), and 59.6% of patients (59 of 99) reported attending at least some college. All patients had metastatic disease. Ninety (88.2%) of the 102 patients received chemotherapy alone or a combination of chemotherapy and surgery and/or radiation as prior treatments (Fig 1). The majority of study participants had gastrointestinal/hepatobiliary (36%; 37 of 102), lung (15%; 15 of 102), pancreatic (8%; 8 of 102), renal (7%; 7 of 102), and head and neck malignancies (7%; 7 of 102).

Overall CAM Use

The overall pattern of CAM use is illustrated in Figure 2. Ninety of 102 (88.2%; 95% CI, 81.6% to 93.1%) patients reported using at least one form of CAM. Of this group, 84 of 90 patients (93.3%; 95% CI, 87.2% to 97.1%) used pharmacologic forms of CAM, most commonly vitamins and minerals (75 of 90; 83.3%; 95% CI, 82.0% to 94.3%). Nonpharmacologic CAM was used by 48 of 90

Table 1. Pharmacologic and Nonpharmacologic CAM Definitions

Pharmacologic CAM
Vitamins and minerals
Vitamin A
Vitamin C
Vitamin E
Vitamin D
Other vitamins (multivitamins in comments)
Betacarotene
Selenium
Nonvitamin, nonmineral preparations
Glutathione
Hydrazine sulfate
Shark cartilage
Coenzyme Q
Aloe
Essiac
Mistletoe
Echinecea
Garlic
Green tea
Ginseng
Other medications
Nonpharmacologic CAM
Diet
Macrobiotic diet
Gerson program
Kelly program
Botanical salves
Juice fasting
Vegetarian diet
Enema and colonics
Other diets
Other CAM therapies
Touch and movement therapy
Mind and emotion therapy
Relaxation techniques
Support/self-help groups
Energy healing
Spiritual healing by others
Other therapies (prayer/faith in comments)
Alternative practitioners
Chiropractor
Nutritionist
Spiritual healer
Holistic/homeopathic
Traditional/folk
Osteopathic
Other alternative medicine practitioner

Abbreviation: CAM, complementary and alternative medicine.

respondents (53.3%; 95% CI, 44.1% to 62.4%). Forty-two of 90 patients (46.6%; 95% CI, 37.6% to 55.9%) used pharmacologic and nonpharmacologic CAM concurrently.

Pharmacologic CAM Use

Vitamins and minerals comprised 89.3% (75 of 84 patients) of pharmacologic CAM use. Vitamins E (48.8%; 41 of 84 patients), C (38.1%; 32 of 84), D (21.4%; 18 of 84), and A (17.9%; 15 of 84) were used frequently, on a daily basis. Thirty-six patients commented that they used multivitamins, with 27 of these 36 patients reporting daily multivitamin usage. Nonvitamin, nonmineral preparations were used by 71.4% (60 of 84) of patients. Green tea was the most popular agent (29.8%; 25 of 84 patients), followed by echinacea (13.1%; 11 of 84) and essiac (9.5%; 8 of 84). Sixty-one percent (51 of 84) of patients consumed vitamins/minerals concomitantly with nonvitamin, nonmineral preparations.

Nonpharmacologic CAM Use

Spiritual methods (individual prayer, faith, or spiritual healing by others) comprised 52.1% (25 of 48 patients) of nonpharmacologic CAM approaches used and 27.8% (25 of 90) of overall CAM use. Other popular nonpharmacologic CAM approaches included touch therapy (12 of 48 patients; 25.0%), relaxation (12 of 48; 25.0%), and support group therapy (8 of 48; 16.7%). Ten percent of CAM users (9 of 90) reported that they had visited a chiropractor at least once, thus making chiropractors the most frequently visited among the nontraditional medicine practitioners.

Characteristics Associated With the Use of CAM

There were no differences between the users and nonusers of CAM in terms of age, sex, tumor site, previous surgery, previous radiotherapy, and level of education; though this analysis is limited given the small number of non-CAM users. A history of prior chemotherapy exposure was weakly correlated with the use of CAM ($r = 0.24$). Among CAM users, prior surgery was weakly correlated with pharmacologic ($r = 0.21$) and concurrent pharmacologic and nonpharmacologic ($r = 0.24$) CAM use. Prior chemotherapy was weakly correlated with nonpharmacologic ($r = 0.26$) and concurrent pharmacologic and nonpharmacologic ($r = 0.21$) CAM use. There was a weak inverse correlation between patients' level of education and pharmacologic CAM use ($r = -0.21$). A subgroup analysis by sex showed that 53.5% (23 of 43) of women combined pharmacologic CAM with other nonpharmacologic approaches as opposed to only 40.4% (19 of 47) of men. In men, prior chemotherapy was moderately correlated with nonpharmacologic CAM use ($r = 0.31$) and weakly correlated with concurrent pharmacologic and nonpharmacologic CAM ($r = 0.28$), and prior radiation therapy was moderately correlated with nonpharmacologic ($r = 0.39$) and concurrent pharmacologic and nonpharmacologic ($r = 0.38$) CAM use. Also in men, previous chemotherapy and radiation combined was moderately inversely correlated to pharmacologic CAM use ($r = -0.31$). Prior surgery and radiation combined was moderately related to nonpharmacologic ($r = 0.30$) and concurrent pharmacologic and nonpharmacologic ($r = 0.37$) CAM use. In women, there was a moderate negative correlation between nonpharmacologic CAM and age ($r = -0.31$); that is, older women used nonpharmacologic forms of CAM less

Table 2. Demographic and Clinical Characteristics of CAM and Non-CAM Users

Parameter	All		CAM Users		Non-CAM Users	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Frequency	102	100	90	88.2	12	11.8
Age, years						
Median	59		59		62	
Range	27-78		27-78		40-78	
Sex						
Male	54	53	47	52.2	7	58.3
Female	48	47	43	47.8	5	41.7
Previous chemotherapy	90	88.2	82	91.1	8	66.7
Education*						
High school	40	40.4	36	40.9	4	36.4
College	59	59.6	52	59.1	7	63.6

Abbreviation: CAM, complementary and alternative medicine.
*Highest level of schooling attended.

frequently than younger women. Combined pharmacologic and nonpharmacologic CAM use was weakly inversely related to age ($r = -0.29$) in women.

DISCUSSION

This study represents the first prospective evaluation of CAM use among patients with advanced malignancies who are enrolled in phase I experimental systemic cancer therapy trials in a large academic cancer center. There are several limitations to the study. The questionnaire could not be entirely anonymous, leading to potential for bias in patient responses. As patients enrolled onto phase I studies generally have disease that is refractory to standard treatment regimens, there is a likely inherent (weak) association with prior systemic chemotherapy. This effect needs to be considered while interpreting the association of the demographic characteristics of CAM use. Although a broad spectrum of patients with varying tumor types was included, there was inadequate ethnic diversity. Ethnicity has been shown to influence patterns of CAM use.[23] More importantly, our sample size was small. Regardless of these limitations, our results can serve as preliminary information to drive more research in this increasingly important facet of cancer care, in the most relevant cancer population, which is those individuals undergoing experimental therapies with unknown toxicity profiles.

Our results demonstrate that nearly 90% of phase I patients seen at the Mayo Clinic use CAM approaches simultaneously with experimental chemotherapeutic therapy. This prevalence rate is consistent with the most recent published report indicating that as much as 83.3% of cancer patients in North America observed in a comprehensive

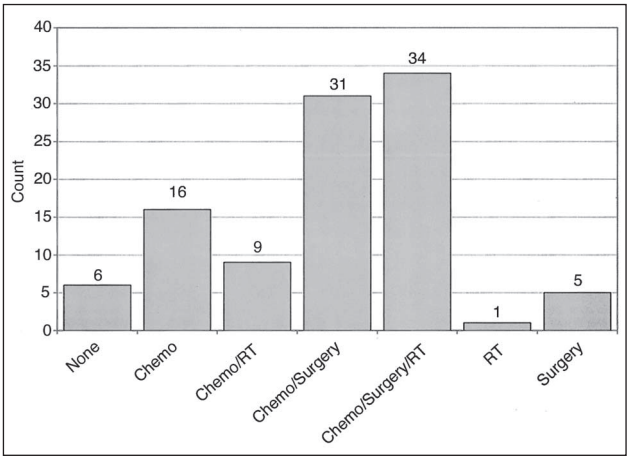

Fig 1. Frequency distribution of the various treatment regimens received by respondents before enrollment in their respective phase I trials. Chemo, chemotherapy; RT, radiation therapy.

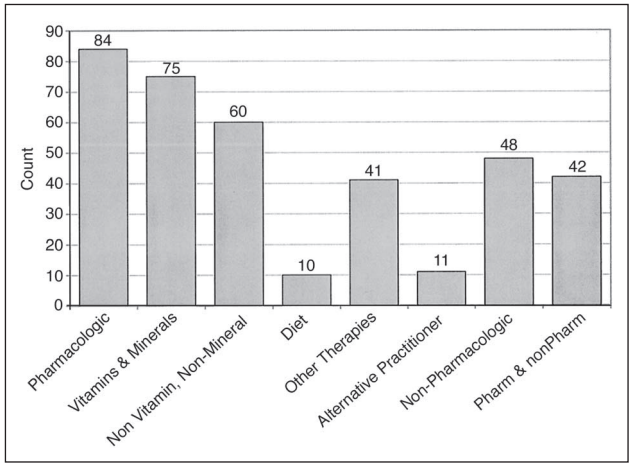

Fig 2. Distribution of complementary and alternative medicine use. Pharm, pharmacologic.

cancer center setting used CAM.[11] Moreover, patients with advanced disease were more likely to use CAM because their condition is incurable.[11,16] As acceptance of CAM by mainstream medicine grows, there seems to be an increasing prevalence of CAM use over time. This could be an actual increase, or alternatively, it may reflect increased awareness of CAM among clinicians.[24]

The demographic factors associated with CAM use found in our study were different from those reported in previous surveys. In previous surveys, CAM use was more predominant in female subjects, younger age groups, and patients with higher levels of education.[11-16] In our survey, we found no association between CAM use and age, sex, or tumor site. Contrary to the earlier reports, there was a weak inverse association between level of education and the utilization of pharmacologic CAM therapies. (Note: this inverse association is for CAM users only; ie, of the patients who used any CAM, the higher level of education meant they were less likely to use pharmacologic CAM). This inverse association, however, is limited by the small sample size of our study compared with the previous surveys. In addition, our survey focused specifically on patients enrolled in phase I clinical trials rather than the broad group of cancer patients. Similar to the findings of Richardson et al,[11] we found prior systemic chemotherapy to be weakly correlated ($r = 0.24$) with CAM usage. There were no differences between men and women in overall CAM use; however, women were more likely to combine both pharmacologic and nonpharmacologic forms of CAM. Spiritual approaches were also cited by 24.5% of all respondents. This suggests that the reason for CAM use extends beyond therapeutic cure but rather indicates emotional and spiritual needs that are not met with conventional medicine.

Pharmacologic agents were the most widely used form of CAM among phase I cancer trial participants, accounting for 93.3% of CAM users. This result is similar to the results of a Canadian survey of breast cancer patients,[15] and is in contrast to the results of Richardson et al, [11] who found that spiritual methods were used by almost 80.5% of the general cancer patient population. Our study, however, confirms earlier data from the general cancer population that indicated that vitamins and minerals were the most frequently used pharmacologic form of CAM. Vitamins E and C were the most widely ingested individual supplements. Green tea, echinacea, and essiac were also quite popular, results similar to the findings of Boon et al.[15]

Green tea, unlike black tea or oolong tea, is the unfermented preparation derived from the leaves and leaf buds of the shrub *Camellia sinensis*. Epidemiologic studies have associated increased consumption of green tea with a reduced incidence of certain cancers, such as breast and prostate cancer. The phytochemicals implicated in its anticarcinogenic property are the polyphenols. The major green tea polyphenols are: (−)-epigallocatechin-3-gallate (EGCG), (−)-epicatechin-3-gallate, (−)-epigallocatechin, (−)-epicatechin, (+)-gallocatechin, and (+)-catechin, which together may constitute 30% of the dry leaf weight. EGCG is believed to be most active component constituent,[25] and it accounts for approximately 60% to 70% of the total catechins[26] in green tea as well. Drug-drug interactions may arise from known pharmacologic properties of green tea. The catechins in green tea have been shown to exhibit inhibitory effects on various cytochrome P450 enzymes, such as CYP1A1, CYP1A2, CYP3A4, CYP2A6, CYP2C19, and CYP2E1.[27,28] Drugs metabolized by these enzymes used in oncology are numerous and include warfarin, benzodiazepines, etoposide (3A4, 1A2, 2E1), vincristine, vinblastine, taxanes, anthracyclines, quinazoline epidermal growth factor receptor tyrosine kinase inhibitors (CYP3A4/A5), estradiol (1A2), and tamoxifen (CYP2E1, CYP3A family substrate). In addition to inhibiting CYP3A4/5 enzymes, catechins are known to induce the phase II drug-metabolizing enzymes glutathione *S*-transferase and quinone reductase.[29,30] High levels of these detoxifying enzymes are known to be one mechanism of resistance to certain chemotherapy drugs such as nitrogen mustards, nitrosoureas, and other DNA damaging agents.

Echinacea herbal preparations are derived from the root and/or aerial parts of the coneflower *Echinacea purpura*, *Echinacea angustifolia*, or *Echinacea pallida*. It is primarily used for its immunostimulatory effect. However, despite the immunostimulatory effect that may be seen with short-term use, chronic long-term use (> 6 to 8 weeks) of echinacea may be immunosuppressive.[31] Leukopenia as a result of echinacea ingestion has been reported.[32] This leukopenia could augment myelosuppressive effects of a wide array of cytotoxic chemotherapeutic agents, leading to severe life-threatening complications. In addition, echinacea is a mild inhibitor of CYP3A4.[33] This property could give rise to drug-drug interactions.

Essiac is a mixture of 4 different herbs: burdock root (*Arctium lappa*), sheep sorrel (*Rumex acetosella*), slippery elm bark (*Ulmus fulva*), and Turkish rhubarb (*Rheum palmatum*) or Indian rhubarb (*Rheum officianale*). Burdock root contains polyphenols and flavonoids (eg, quercetin) that have variable effects on the modulation of cytochrome P450 activity. For example, quercetin is a known potent inhibitor of CYP3A. Moreover, quercetin demonstrates synergistic cytotoxic effects with certain chemotherapeutic drugs, such as cisplatin.[34] Anthraquinones found in both sheep sorrel and Turkish rhubarb,[35] such as aloe emodin, emodin, and rhein exhibit cytotoxic and immunosuppressive properties. Emodin has been shown to inhibit tyrosine kinase activity of the HER2/*neu* receptor as well as to show synergistic antiproliferative activity against HER2/*neu* expressing cells when used in combination with cisplatin, doxorubin, and etoposide.[36]

These findings lead us to conclude that use of CAM therapies is widespread among phase I cancer trial participants. From the brief discussion above, it is clear that pharmacologic CAM agents have real potential to interact with experimental therapies to affect toxicity and/or efficacy. More research is needed in the pharmacology of the most commonly used CAM agents and their potential for metabolic, pharmacokinetic, and pharmacodynamic interactions with experimental cancer agents. Above all, phase I investigators should pay close attention to the use of these nonphysician-prescribed agents and clearly document them in patient records. This will make it possible to identify potential drug interactions leading to unusual toxicities by reviewing patients' concurrent medications.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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