Research of Complementary/Alternative Medicine Therapies in Oncology: Promising but Challenging

By Mary Ann Richardson

AN ESTIMATED 50% OF cancer patients use complementary/alternative medicine (CAM), and most patients combine CAM with conventional medicine.[1-5] A summary of 26 surveys conducted across 13 countries estimated the prevalence of use at 31.4% and ranging from 7% to 64%.[6] A prospective study reported that 28.1% of breast cancer patients (n = 480) initiated CAM use within 12 months of treatment, but use was associated with greater psychosocial distress.[5] In the general population, CAM use has literally exploded since the surveys conducted in the early 1990s. Between 1990 and 1995, CAM use rose from 33.8% to 42%, and visits to CAM practitioners increased from 427 to 629 million; out-of-pocket expenditures were estimated at $27 billion.[7,8] Accompanying this increased public interest,[7,9] however, is a growing demand for systematic evaluations of safety and efficacy.[10-13]

Rigorous scientific testing is of vital importance. In response to this demand, the Office of Alternative Medicine (OAM) was established at the National Institutes of Health (NIH) in 1991 by congressional mandate. In 1993, OAM funded 30 pilot studies at $30,000 each. Despite these limited resources, the response was the largest in the history of the NIH and resulted in over 6,000 requests for applications, 800 letters of intent, and 452 applications. Given the overwhelming interest by the research community and with continued congressional support, OAM expanded their research base in 1995 to 10 exploratory research centers at major medical centers. With continued public support, OAM was upgraded to the National Center for CAM (NCCAM) in 1998, and again, they expanded their infrastructure with three new centers using the P-50 funding mechanism.

Since the first research initiative by OAM, a multidisciplinary team at the University of Texas M.D. Anderson Cancer Center (MDACC) and the School of Public Health has been dedicated to applying rigorous research methodology to systematically evaluate CAM approaches. In one of the first pilot studies, this team used the randomized controlled trial design to assess the impact of support groups versus imagery/relaxation on immune function, quality of life, and coping for women who had undergone treatment for breast cancer.[14-16] Subsequently, The University of Texas–Center for Alternative Medicine (UT-CAM) was established as one of the exploratory research centers in 1995. The primary aims of the center were to evaluate the efficacy of biopharmacologic and herbal therapies for cancer prevention and treatment, establish a network of CAM practitioners and researchers for collaborative research, and improve self-assessment skills of CAM practitioners and researchers.

The purpose of this article is to review the state of CAM research in cancer, summarize activities underway at UT-CAM, NCCAM, and the National Cancer Institute (NCI), and highlight positive and challenging aspects of investigating this area.

ASSESSING THE STATE OF THE SCIENCE

The first task for UT-CAM was to assess the state of the science and establish a research agenda. UFCAM used multiple sources to identify agents, including major reports by the NIH,[17,18] comprehensive books on CAM approaches,[19-21] national surveys of CAM use, and consultations with experts in the field. Subsequently, over 30 therapies were identified for review and categorized as either herbal, biologic, pharmacologic, or integrated regimens.

The systematic review entailed an exhaustive search of library databases, including MEDLINE, Cancerlit, Embase, and Current Contents. These searches were expanded by information from the Internet, reviews of CAM journals and books, site visits, unpublished documents, and information from CAM proponents. The review yielded approximately 6,000 references; 58.8% were applicable to cancer. Approximately 2,400 articles (69.0%) were retrieved and categorized as human, animal, and in vitro studies, reviews, and other information (Table 1).

A working set of agents was classified by research methodology and the accumulation of evidence. We assume that the credibility of study results and, thus, their potential impact on therapeutic practice can be judged by the methods used to generate and interpret those results. Therefore, a continuum of research methods and treatment decisions exists. As the rigor of research methodology improves, the

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Table 1. CAM Referenced and Coded by Category and Topic

Therapy Categories	Human	Animal	In Vitro	Reviews	Other	Total
Herbal/plant therapies	196	427	320	56	294	1,293
Biologic/organic therapies	213	99	108	40	238	698
Chemical/pharmacologic therapies	44	76	62	31	125	338
Special regimens/integrated systems	15	1	6	12	67	101
Total	468	603	496	139	724	2,430

strength of evidence increases. Therefore, clinical studies were classified by research methodology (ie, randomized trials, prospective or retrospective cohort studies, case control, clinical series, care reports) and summarized in annotated bibliographies (Table 2).

We believe that advancing the level of systematic investigation for CAM agents will ultimately benefit the public as information becomes more reliable. The current assessment of the science is presented for the general public and medical community on the UT-CAM Web site (http://chprd.sph.uth.tmc.edu/utcam/). This site has been recognized as a premier source of reliable information on CAM therapies for cancer.[22-24]

READINESS OF CAM FOR RESEARCH

Regardless of their level of acceptance by mainstream medicine,[11,13,25,26] these therapies have infiltrated every aspect of health care, and many believe that access should be part of standard oncologic treatment.[27] At the most basic level, evidence of efficacy is required before these therapies are moved into clinical testing.[28] For many CAM agents, characterization of the product, standardization, reproducibility, safety, and information on basic pharmacology are lacking, while evidence of efficacy rests on anecdotal reports. Others suggest that if the prior probabilities of CAM hypotheses are not higher than those of competing conventional hypotheses, a rationale for testing does not exist.[26] Therefore, developmental work has been necessary to educate the CAM community on the requirements for clinical testing (ie, the Investigation New Drug Application) as well as standards of rigorous research. Furthermore, dialog between the conventional research and CAM communities is necessary because the CAM community must be involved in these investigations. We would not expect a researcher who has no experience with surgery to design a study without consulting a surgeon. Neither should we presume to design studies of CAM without involving CAM practitioners.[29]

Over the past 4 years, UT-CAM has worked with the CAM community to develop clinical protocols, initiate basic in vitro and in vivo testing, conduct epidemiologic historical cohort studies, and pilot test the prospective outcomes evaluation and monitoring system (POMES) process. Clinical studies ranging from small pilot feasibility studies to randomized phase III trials are in progress to test nutritional and herbal supplements that are widely used by cancer patients and have a rationale for assessment. A summary of this research is presented by category.

Epidemiologic Studies

Survey of CAM use. A survey conducted in eight clinics at MDACC (n = 460) assessed use of CAM. Overall, 83% of patients used CAM. The most frequently used approach was the use of herbs and/or vitamins (62%). Overall, 64.5% did not discuss CAM with providers because they were uncertain of the benefits (54.0%) or because physicians never asked (47.6%).[30]

Pattern of use of an herbal tonic. In a population-based survey of North America, we assessed the characteristics of consumers of a popular herbal tonic (Flor●Essence; Flora

Table 2. Human-Related Studies Coded by Therapy and Study Design

Therapy	RCT	Cohort*	Case Control	Clinical Series	Case Report	Total
Herbal						
Aloe	1	0	0	0	0	1
Cat's claw	0	0	0	2	1	3
Coriolus versicolor	14	8	0	2	0	24
Essiac	0	0	0	0	4	4
Garlic	0	5	6	1	0	12
Green tea	0	1	13	3	0	17
Hoxsey	0	1	0	0	1	2
Mistletoe†	5	9	0	12	8	34
Saw palmetto	9	0	0	2	0	11
Traditional Chinese medicine	26	9	2	36	5	78
Biologic/organic						
Cartilage	0	0	0	8	1	9
CoQ10	1	7	6	6	4	24
Coley toxins	3	16	0	7	1	27
Govallo	0	0	1	0	1	2
Homeopathy	0	0	0	0	5	5
IAT	0	0	0	1	1	2
Melatonin	17	7	15	56	1	96
MTH-68	0	5	6	3	6	20
Selenium	7	3	11	7	0	28
Chemical/pharmacologic						
714X	0	0	0	0	4	4
Antineoplastons	0	0	0	17	2	19
Hydrazine sulfate	8	0	0	10	3	21
Special regimen/integrated system						
Gerson	0	3	0	0	2	5
Livingston-Wheeler	0	2	0	0	0	2
Macrobiotics	0	1	0	0	2	3
Revici	0	1	0	1	3	5
Total	91	78	60	174	55	458

*Prospective and retrospective cohort studies.

†Additional studies (n = 10) of mistletoe were not in German and not coded.

Manufacturing and Distributing, Ltd, Burnaby, British Columbia, Canada). Preliminary results from responders (n = 4,708) indicate they are predominately white, married, college educated, and aged 61 years old (SD, 14.4 years). Most individuals are current or former cancer patients (75.5%) and use the tonic as a medical treatment (62.8%), for prevention (34.1%), or to control symptoms (21.3%). Among the 725 cancer patients (response rate, 52%) who responded to a more detailed survey, half (53.2%) reported that the tonic offered hope, whereas many expected the herbs to improve immune function (75.8%), prolong life (59.2%), improve quality of life (54.0%), or cure the cancer (48.9%).

Retrospective comparison. With the appropriate documentation and follow-up, retrospective reviews are possible and allow testing for a signal that the treatment is of benefit. This epidemiologic study retrospectively compared the experience of patients treated with endotoxin therapy to that of patients treated with standard care.[31] Using a Cox proportional hazards model with time-dependent covariates, the survival experience for patients treated with Coley toxins, as identified from monographs prepared by Helen Coley Nauts, was compared with that of patients from the Surveillance, Epidemiology, and End-Results database who received surgery only. Our results suggest that risk of death was not significantly higher for Coley toxin–treated patients in the following disease sites: kidney (hazard ratio [HR], 1.2; 95% confidence interval [CI], 0.2 to 6; $P < .79$), ovaries (HR, 0.9; 95% CI, 0.2 to 4.3; $P < .94$), breast (HR, 0.7; 95% CI, 0.4 to 1.3; $P < .24$), and soft tissue (HR, 1.3; 95% CI, 0.7 to 2.3; $P < .38$).

Field investigations. Efforts by the UT-CAM and NCCAM resulted in over two dozen investigations nationally and internationally. Meeting in the CAM practice sites provided information on the feasibility of collecting relevant information from patient records and determining follow-up status. Two well-established CAM clinics—the Bio-Medical Clinic in Tijuana, Mexico, and the Livingston Clinic in San Diego, CA—were investigated by UT-CAM. Most patient records were complete at the Livingston Clinic, but they were not at the clinic in Mexico. However, follow-up at both clinics was below tumor registry standards, and comparison with Surveillance, Epidemiology, and End-Results data was not feasible (Richardson et al, unpublished data).

Preclinical Studies

Natural product extracts. In a series of studies of green tea polyphenols, UT-CAM collaborators developed and validated high-performance liquid chromatography (HPLC)/electrochemical detector–based assays to determine catechin levels (ie, epigallocatechin gallate) in the green tea extract. This analytical method, together with a method to assay caffeine levels, provided data on clinical pharmacology for the extract in an ongoing phase I/II trial at MDACC.[32,33]

In vitro tests of the whole plant extract of mistletoe suggested that mistletoe lectin III, one of the primary active components in the whole plant extract, mediated cytotoxicity through distinct killing pathways. Mistletoe lectin III preferentially affected $CD8^+$ cells with a memory phenotype but did not induce sister chromatid exchange–inducing DNA lesions. The extract reduced the intensity of telomeric signals, increased the frequency of telomeric association and C-anaphases, and reduced nuclear Bcl-2 and p53 proteins. The study cannot exclude the possibility that these effects were due to a decrease in nuclear p53 proteins.[34]

Over the past year, extensive developmental research on the water-soluble extract of oleander has led to characterization of the plant extract by HPLC and electrochemical detection of the carbohydrate content. A carbohydrate fingerprint has been developed to monitor quality control and stability by the CarboPac HPLC column (Dionex Corp, Sunnyvale, CA), and nonpolar compounds have been isolated to identify the two most potent cytotoxic molecules.

Ginseng saponins. After a dose-finding study, two protocols tested the ability of Korean red ginseng saponins to modulate carcinogenic metabolism and have an impact on progression of established and developing precancerous lesions in the rat colon. Compared with the carcinogen-only controls, ginseng significantly ($P < .05$) reduced aberrant crypt foci, by 25%, in the low-dose group (0.1 g/kg) but not in the high-dose group (1 g/kg). Ginseng had no apparent impact on developing precancerous lesions.

Purified plant-based products. Collaborative research with CAM proponents has assessed the potential role of purified plant-based herbal supplements and related products (ie, emodin, ellagic acid, resveratrol, and genistein) in the prevention or treatment of cancer. After determining their relative cytotoxicity in human breast and prostate cancer cell lines, these products will be combined in a logical effort to test the synergism between specific plant products. We plan to optimize the relative chemopreventive activity of the combined plant products. Although the project is an exploration of in vitro pharmacology, if promising, combinations of agents could be tested for chemopreventive or antitumor activity in vivo.

Isolated marine-based biologic agents. In vitro studies of dolastatin-10, a product isolated from a shell-less mollusk, *Dolabella auricularia*, assessed chromosome morphology, telomeric associations, and induction of polyploidy and cell death in a metastatic murine melanoma cell line. The observations suggest that dolastatin-10 could be a potent antineoplastic agent against malignant melanoma based on

(a) increased frequency of metaphases, with telomeric associations, (b) induction of clumping in metaphase chromosomes, (c) induction of polyploidy, (d) formation of multinucleated cells, and (e) induction of cell death. In addition to interaction with cell microtubules, the mechanism of action may be mediated by loss of telomeric repeats and the induction of chromosome aberrations.[35]

A series of experiments are underway to isolate and purify the active inhibitor of 5- and 12-lipoxygenase (LOX) enzymes from an extract of the sea cucumber (phylum Echinodermata, class Holothurioidea), a marine animal. Studies to evaluate the effectiveness in blocking the LOX enzymes are necessary, because these enzymes have been shown to accelerate cancer progression and metastatic formation in animal models. Inhibitors of the LOX enzymes, involved in the metabolism of arachidonic acid to leukotrienes, represent an exciting, novel therapeutic target for the treatment and prevention of cancer. Cell culture studies clearly implicate a role for inhibitors of 5-LOX in the treatment of prostate and lung cancer.

Coenzyme Q10 (ubiquinone). A series of in vitro experiments tested the relative cytotoxicity of coenzyme Q10 (CoQ10) in a human breast cancer cell line and examined the impact of CoQ10 on the cytotoxicity of standard chemotherapeutic agents (ie, doxorubicin, paclitaxel, and cisplatin) and the new proteasome inhibitor (PS273). Preliminary results suggest that CoQ10 did not affect the relative toxicity of the standard agents; however, CoQ10 may augment activity of PS273. Additional studies are necessary, specifically testing the impact of CoQ10 on the doxorubicin apoptosis–mediated pathway.

Clinical Studies

Melatonin. In a randomized phase III study at MDACC, UT-CAM is testing the impact of the melatonin (20 mg daily) on the hematopoietic toxicity of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy in patients with large-cell lymphoma. We will evaluate melatonin's possible impact on response rate, disease-free survival, and overall survival.

Mistletoe. A pilot study (n = 10) at Wellesley Hospital, affiliated with the University of Toronto, is testing the feasibility of recruiting and administering a whole-plant mistletoe extract to patients with advanced, unresectable, or recurrent (stage IIB, III, or IV) esophagus cancer. Measures of quality of life, clinical benefit, and toxicity are being monitored, but no preliminary data are available.

Herbal tonic. A randomized, parallel, phase II pilot study is being finalized for patients with advanced colon cancer who present for palliative chemotherapy (ie, fluorouracil and folic acid). The pilot study will be the first clinical assessment of the herbal mixture Flor●Essence, which is widely used by cancer patients with anecdotal reports of improved well-being and survival. The study will allow us to monitor the willingness of patients to accept randomization and to evaluate compliance, safety, and toxicity.

Shark cartilage. In collaboration with a Canadian biotechnology company, a multicenter, phase I/II trial was completed of whole cartilage extract for the treatment of lung, prostate, and breast cancer. The phase II trial in refractory lung cancer reported a positive trend in favor of a dose-response (ie, there was an impact on analgesic consumption, weight loss, and tumor progression). The number of patients with stabilization of tumor was 38% higher at the upper dose levels, and median survival was superior to the expected 25 weeks.[36]

Prospective Monitoring Studies

One possible approach to obtain data on CAM therapies is the POMES process proposed by the NCI and NCCAM. The process is comparable to a classic phase II trial but includes three components unique for CAM investigations. Practitioners of CAM deliver the therapy in the context of their clinical practice, a monitoring board of conventional oncologists confirms patient eligibility and assesses outcomes, and a research team monitors compliance, patient follow-up, and outcomes assessment. In a pilot study of patients (n = 10) who elected to be treated at an integrated CAM treatment facility in Vancouver, British Columbia, Canada, we will assess the feasibility of the POMES process in collaboration with the Tzu Chi Institute for Complementary and Alternative Medicine and clinicians from the British Columbia Cancer Agency. Patients with pathologically confirmed advanced cancer who consent to participate in the study will be monitored for safety, biologic markers, disease progression, survival, and performance status.

RESEARCH PLANNED BY NCI AND NCCAM

Phase III Clinical Studies

A phase III pivotal trial is being finalized with support from NCCAM and NCI to assess the benefit of shark cartilage for patients with nonoperable, stage IIIa and IIIb non–small-cell lung cancer. The trial will be conducted through the MDACC network in collaboration with the Ottawa Regional Cancer Center in Canada. The primary end point will be survival, with time to progression and quality of life as secondary end points. Testing for another cartilage product is being planned at another major cancer center in the United States. The comprehensive cancer center at New York Columbia Presbyterian Cancer Center has begun a phase III trial to test a complex treatment regimen consisting of vitamins, enzymes, diet, and detoxification against standard treatment for advanced pancreatic cancer.[37]

Cancer Advisory Panel for Complementary Alternative Medicine.

The Cancer Advisory Panel for Complementary Alternative Medicine is a joint initiative of the NCCAM and NCI. The panel's key role is to serve in an advisory capacity in the assessment of present and future CAM clinical trials and medical interventions, determine potential research opportunities, and develop a mechanism for communicating research results from these studies to key constituencies. The 15-member panel consists of oncologists, surgeons, CAM practitioners, research methodologists, and experts in the area of CAM.[38]

CHALLENGES FOR INVESTIGATIONAL CAM THERAPIES

According to our experience over the past 4 years, the majority of herbal and nutritional supplements are not fully developed or ready for definitive trials, despite wide use by cancer patients. Most whole-plant extracts and commercial teas rarely have data on product characterization, standardization, or stability.[39] Furthermore, the optimal dose, schedule, and route of administrative have rarely been determined. As indicated by the research activities of UT-CAM, preclinical, pharmacokinetic testing and developmental phase I/II studies are necessary before these products can be launched into definitive clinical trials.

Studies in this area must be subjected to the highest standards for design, implementation, and evaluation. Clear hypotheses should be identified a priori and tested in methodologically sound studies with adequate sample sizes to provide sufficient power to detect an effect should it exist. Researchers may face problems accruing patients to randomized clinical trials, considered the gold standard of biomedical research. Strict exclusion criteria and barriers to participation may limit accrual, which will decrease the study power and limit generalizability of the findings.[16] Several studies of CAM have reported difficulty with accrual. In a trial underway to test an herbal formula with placebo to mitigate the side effects of chemotherapy, women who want to use the herbs are refusing randomization. They can purchase these products in the market.[40] In another trial comparing standard palliative therapy with a complex CAM regimen (ie, nutritional supplements, enzymes, diet, and detoxification), patients with pancreatic cancer are either willing to comply with this complex regimen or prefer the standard treatment. Thus, willingness of patients to accept randomization is a challenge. Should patients accept randomization, the availability of CAM agents in the open market may result in the contamination of the control group. Finally, with fewer than 3% of all cancer patients participating in clinical trials of conventional treatment, researchers designing trials of CAM may encounter limited access to patient populations.

In contrast, options for patients with advanced disease should be expanded, as palliation is often the only treatment and quality of life the only therapeutic end point. Patients with advanced solid tumors often have a poor prognosis, and many are not candidates for curative approaches. Quality of life for these patients is often limited by the disease or toxicities associated with treatment. When cure is not an option, oncologists aim for palliation to relieve symptoms. CAM therapies may be beneficial for these patients.

Regardless of the stage of disease, reliable information on CAM therapies is needed for the public, physicians, and other health care professionals. The challenge to the CAM community, therefore, is the acquisition of data on patient outcomes and the preparation of their products for clinical testing, when appropriate. To move this field forward, state-of-the-art, rigorous evaluations are needed with mutual respect and open dialog between CAM practitioners/proponents and the scientific community. The developmental, pilot work reported here reflects a step toward establishing those collaborative links and moving forward with trials.

The investigations of mistletoe, melatonin, and the Flor●Essence herbal tonic are important because they represent the first clinical trials of their kind in North America. They should provide preliminary data on safety, efficacy, and the feasibility and rationale for further testing. The phase I/II and in vivo studies of cartilage were critical because they established a foundation and collaborative relationship to move forward with a definitive, phase III trial of this agent. The preclinical studies provide information on the efficacy of herbal and nutritional supplements and may serve as templates for examining possible chemopreventive activity or interaction with standard cytotoxic agents.

In summary, investigations by UT-CAM represent the application of scientific, rigorous research by established, conventional oncologists and researchers. This preliminary data and field experience are prerequisites for larger, more definitive trials. The strategy of UT-CAM has been to move agents forward along the research continuum, from basic research to pilot/feasibility studies to phase I/II studies, that is, to increasingly more rigorous research designs. Although many are calling for definitive trials of efficacy, this field is in its infancy. In the meantime, the patients and public are eager for any information. They will continue to influence policy makers to allocate resources for CAM research. It is their money and their disease, and we must begin to build bridges between rigorous science and CAM.[41] With continued support by the NCCAM and NCI, dedication of CAM research centers, and willingness of the oncology and CAM communities to do the research, we can move the field from alternative to evidenced-based medicine.

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