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Ethical and Clinical Controversies in Hematology

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Integrative Medicine in Hematology/Oncology: Benefits, Ethical Considerations, and Controversies

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Integrative Medicine (IM), a newly emerging field, has evolved from Complementary and Alternative Medicine (CAM). CAM refers to diverse medical and health care systems, practices, and products that are not presently considered part of conventional medicine and generally have limited scientific evidence. In the US, CAM is a multi-billion dollar, unregulated industry with potential benefits and risks to consumers, including cancer patients, who are high utilizers of complementary therapies. Patients' CAM use often is unsupervised by physicians, yet patients need the advice and guidance of their hematologists/oncologists as part of total cancer care. Ethical and legal issues physicians need to address include inquiring about and educating patients regarding potential interactions (e.g., drug-herb, radiation-antioxidant) or product contaminants, while discussing other therapies that may alleviate symptoms and/or improve quality of life. Administratively, CAM offerings in medical settings require relevant policies and procedures, such as properly credentialing practitioners and providing financial assistance counseling for those who cannot afford fee-for-service. Unlike "Alternative Medicine," the goal of IM is to combine mainstream medical therapies and CAM therapies (e.g., acupuncture, meditation, music therapy) that have some high-quality scientific evidence of safety and effectiveness. The Society for Integrative Oncology (SIO), a new international organization of oncology professionals studying and integrating effective complementary therapies in cancer care, serves as a forum for presenting scientific data on these therapies while emphasizing the importance of developing infrastructure that promotes IM principles and practices. The ultimate goal is to develop multidisciplinary expertise and therapeutic synergy between conventional and complementary therapies.

What is Integrative Medicine (IM), how is it clinically relevant, and what is its importance to hematologists and oncologists in their clinical practice? As a recently emerging field, IM has evolved from the more familiarly known Complementary and Alternative Medicine (CAM). However, IM differs from CAM in two important ways. First, whereas CAM describes a broad array of therapies that are used in conjunction with or instead of conventional mainstream treatment, IM combines mainstream medical therapies and CAM therapies. Secondly, CAM includes therapies that are proven and others that have little or no scientific basis, while the goal of IM is to incorporate complementary therapies for which there is some high-quality scientific evidence of safety and effectiveness.[1] Yet in order to

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understand the role of IM, it is important to understand its underpinnings in CAM. Over the past several decades, CAM has had a dramatic history in its nomenclature, increasing use by patients and the public, and emergence as part of total patient care.[1-3]

The terminology itself, "Complementary and Alternative Medicine," has created significant difficulties in acceptance by physicians and other health professionals as a scientifically sound approach. Historians of this discipline would describe how far the field has evolved in the past 30 years, from a time when the scientific community often referred to such interventions as "Quackery."[2] Since then, descriptive terms used by clinicians and researchers have shown a gradual trend toward acceptance from the Western medical community, while retaining a commitment that holds these therapies to a standard of scientific scrutiny: e.g., from "Questionable Methods of Therapy" to "Unorthodox," "Unconventional" and "Unproven" Methods. The current designation "Complementary and Alternative" medicine includes therapies that are used in combination with conventional treatments, some of which may be safe, while others may be unsafe.

Overview—Complementary and Alternative Medicine

What then is "CAM"? As defined by the National Center for Complementary and Alternative Medicine (NCCAM), CAM is "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. While some scientific evidence exists regarding some CAM therapies, there are key questions that are yet to be answered through well-designed scientific studies—questions such as whether these therapies are safe and whether they work for the diseases or medical conditions for which they are used."[1] "Complementary" refers to those practices used together with conventional therapies, while "alternative" applies to those practices that are used in place of conventional practices. The CAM domains include: 1) alternative medical systems such as homeopathy and naturopathy as well as culturally based systems such as Traditional Chinese Medicine and Ayurvedic Medicine; 2) mind-body interventions such as yoga, prayer, and meditation; 3) biologically based systems such as diets and herbs; 4) manipulative and body-based practices such as massage and chiropractic manipulation; and 5) energy therapies such as Reiki, QiGong, and magnets.[1]

CAM use is widely prevalent, but its potential positive and negative impact on patient care is not well understood by patients or their health care providers. In the United States, CAM has become a multibillion dollar unregulated industry (in 2005, roughly a 40 billion dollar industry), with the costs incurred almost totally by consumers, who simultaneously face the risks of unsupervised use. Cancer patients are among the highest users of CAM therapies. It has been estimated that up to 83% of patients with a broad range of cancer diagnoses use CAM.[3-8] In one representative study, the predominant choices of CAM therapies were vitamins and herbs, followed by movement and physical therapies, such as exercise, massage, and chiropractic manipulation.[4] The expectations of cancer patients are that CAM offers symptom management, improved quality of life and, in some cases, the hope of lessening the disease process and potential cure.[4,9,10] Whether the particularly high CAM use for cancer patients is due to such factors as individual cultural and/or ethnic background, the nature of the illness, greater availability of these products and services, and desire for increased sense of control and holistic care, other studies of a wider range of patients seeking treatment have demonstrated similar findings regarding interest in and use of CAM.

Patient-Physician Communication Regarding CAM

Despite the high CAM usage by patients, there is often a gap in communication and mutual understanding of CAM between patients and their physicians; sometimes patients are unaware of certain therapies that could benefit them, while in other cases, patients use unsupervised therapies with potentially serious implications. It is well documented in the medical literature that communication between patients and their physicians regarding CAM use does not occur routinely. In one study, of the 70% of CAM users who were receiving concurrent conventional and CAM treatment, 63%-72% did not disclose their CAM use to their physician.[11] In this survey, the most common reasons patients cited for nondisclosure were: 1) that it was not important for their physician to know about their CAM use (61%) or 2) that their physician never asked about CAM use (60%). Additional responses, from among choices provided, included, "It was not the doctor's business" (31%) and "The doctor would not understand" (20%). Only 14% of respondents overtly identified that their doctor would disapprove and discourage use.

Other studies support patients' perception that physicians are not knowledgeable about CAM therapies, such as herbs. In a survey of dietary supplement use by patients, 44% of users believed their physician knew little about these over-the-counter products. Additionally, 72% reported they felt strongly enough about the potential health benefits of supplements that they would continue to use them even if they were shown to be ineffective in scientifically conducted clinical studies. Nonetheless, they supported government regulation of the products regarding safety and the accuracy of advertising claims.[12]

In the past decade, CAM practices increasingly have gained the attention and interest of the biomedical research community, in part due to the infusion of money for research by the federal government. The major governmental biomedical research agency, the National Institutes of Health (NIH), first established an Office of Alternative Medicine (OAM) in 1992, based on a congressional man-

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date, with an initial annual budget of 2 million dollars. In 1998, OAM was expanded to become the National Center for Complementary and Alternative Medicine (NCCAM), with a $50 million budget. Along with the Office of Cancer Complementary and Alternative Medicine (OCCAM), a division of the National Cancer Institute (NCI),[1,13] these two centers sponsor and support cancer research in CAM. Having sources of federally funded, peer-reviewed research in CAM has expanded medical professionals' knowledge and education about these modalities. Furthermore, it has helped to establish the legitimacy of CAM as the subject of scientific inquiry, moving the field forward through greater cooperation between clinical investigators and CAM practitioners.

Evolution of CAM into Integrative Medicine

"Integrative Medicine" is a more recent term promoted by many proponents of complementary therapies in the west.[1,2] Integrative Medicine (IM), as defined by NCCAM, combines mainstream medical therapies and CAM therapies for which there is some high-quality scientific evidence of safety and effectiveness.[1] In an oncology context, IM emphasizes the incorporation of complementary therapies (e.g., acupuncture, meditation, music therapy) with conventional treatments, such as surgery, chemotherapy, and radiation. CAM was initially patient-driven and, as previously stated, there exists a lack of communication between physician and patient despite the high interest in and use of complementary therapies by patients. These therapies need to be part of a patient-physician dialogue, because the therapies may positively or negatively impact treatment decisions, medical issues, or a patient's overall sense of well-being. Integration also means that patients, their clinicians and CAM providers are working closely together. In most cases, the hematologist/oncologist, as the primary coordinator and conductor of the patient's care, needs to be aware of all the care that the patient receives. When complementary therapies are effectively combined with conventional therapies in order to address the patient's whole being and experience, the primary care physician is helping to meet the patient's total needs. Examples of this assimilation of therapies involve the recognition of evidence-based treatment options of complementary therapies, with the assurance that they satisfy a risk-benefit analysis and are safe and efficacious. Physicians need to convey to patients that integrative therapies are providing supportive and preventive care and are not being promoted as a "cure" or as an alternative to conventional therapies when effective treatment is available. As one patient expressed, "Integrative medicine is like building bridges between patients and their physicians." The judicious use of complementary therapies together with conventional therapies within a therapeutic and empathic doctor-patient relationship helps to ensure that the patient is treated as a whole person.

Ethical and Therapeutic Considerations

In the new discipline of IM, emerging questions need to be addressed by the physician/specialist. What are some of the CAM practices utilized in the community to address prevention of malignancies, to lessen side effects during chemotherapy, radiation therapy, and/or to support patients during rehabilitation and beyond? There are ethical and legal issues that clinicians need to be aware of as part of a balanced treatment approach.[14,15] For example, patients may consume herbs that alleviate some cancer symptoms, but also may contain constituent chemicals within the product that have unknown intrinsic effects or side effects due to contaminants.[16] In addition to the well-recognized problem of drug-drug interactions, there are other interactions, such between drugs and herbs and between antioxidants and chemotherapy and/or radiation therapy, that could interfere with treatment effectiveness.[17-20]

In establishing integrative medicine centers, whether in a hospital, ambulatory setting, or in a group practice, policies and procedures need to be established and observed. How does an organization credential CAM practitioners? What complementary therapies should be offered? When should complementary therapies be recommended to our patients? How are treatment decisions made? How are complementary therapies evaluated? Who is responsible for an adverse event? Since many complementary services are not covered by insurance and require payment on a fee-for-service basis, how does one create a financially viable program of IM, while providing services without discrimination regarding a patient's income? These are just a few of the ethical and legal issues that must be addressed.

Guidelines for Physicians Advising Patients

To advise their patients, the primary care hematologist/oncologist needs knowledge about which complementary therapies can be recommended or accepted, and which should be discouraged. The guidelines for advising patients should be based on evidence and efficacy.[21,22] Therapies that may be recommended should have evidence that supports both efficacy and safety, e.g., acupuncture. In a study of 34,407 acupuncture treatments, there were 43 minor adverse events and no serious events.[23] The minor events involved mild local discomfort and some local bleeding at site of a needle. Thus, acupuncture has been proven to be safe.[24] Acupuncture is a therapy that is well tolerated by cancer patients, including those on anticoagulation therapy, if they have adequate laboratory values and modifications of standard techniques are made. What is the efficacy of acupuncture? The NIH consensus on acupuncture and several controlled, randomized trials have demonstrated positive results of acupuncture for controlling chemotherapy-induced nausea and vomiting.[25-28] Therefore, evidence supports recommending acupuncture for this use.

Therapies that should be discouraged are those that have no evidence of efficacy and have a serious risk. Such therapies include well-studied drugs such as laetrile and

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hydrazine sulfate, as well as more recently studied supplements such as shark cartilage, all of which have shown to be both ineffective and toxic.[29-31] In between these two ends of the spectrum is a category of therapies that may be accepted, where the evidence on efficacy is inconclusive, but the evidence does support safety. Examples of this category of complementary therapies are acupuncture use in cancer pain, radiation-induced xerostomia, post-chemotherapy fatigue and/or in insomnia and anxiety, massage for anxiety and stress, and nausea in the case of autologous marrow transplantation.[32-36]

There are several areas where therapies should be discouraged or advised as unacceptable, besides the direct toxicity exemplified by laetrile or hydrazine sulfate. Some CAM therapies can reduce the effectiveness of conventional therapies; others can interact with other drugs and cause serious life-threatening side effects. Sometimes the use of CAM therapies for some symptoms can forestall the patient from getting known effective therapy for an underlying serious problem such as a malignancy. St. John's wort is used currently for the management of symptoms of depression, but recent randomized controlled trials show its effect to be comparable to a placebo.[17, 21] Disconcerting, however, is the fact that St. John's wort can reduce the effectiveness of drugs like cyclophosphamide and cyclosporine.[17,18,21] Evidence suggests that St. John's wort, garlic, gingko, echinacea, ginseng and kava modulate cytochrome P450 isozymes and can reduce the levels of many important antineoplastic drugs such as cyclophosphamide[17] (**Table 1**). There are also potential drug-herb interactions that can accentuate a toxic event. For example, the use of garlic, ginkgo or ginseng together with anti-platelet agents can accentuate bleeding.[31] Reports of unusual side effects of chemotherapy and/or a lack of a response to a known effective agent should alert the clinician to the possibility that the patient may be taking herbs or botanicals in addition to their conventional therapy. Likewise, symptoms suggesting a drug allergy should cause the clinician to inquire about the use of herbs/supplements. Antioxidants are among the frequently used over the counter products promoted for use for chronic diseases or prevention, but guidance on their use with chemotherapy and/or radiation therapy remains controversial.[19, 20]

Educational Resources

There are a number of reliable databases that can be accessed by physicians with information about the benefits and side effects of herbs and botanicals, while also providing data on drug-drug and drug-herb interactions.[1,13,37-42] Education of physicians is being stimulated by the widespread use of herbs and botanicals by patients and the concern for their patients' safety. In a recent survey of 20 physicians at a cancer center, 50% seldom ask their patients about CAM therapy use, while 60% stated that their patients often ask them about CAM. Physicians stated that their biggest concerns were that they lack familiarity with their services and products and lack data on evidence (D. Rosenthal, unpublished data). Courses and training opportunities, as well as workshops at national meetings, are available for physicians and other health professionals interested in complementary therapies. Moreover, many medical schools and academic health centers have incorporated CAM education and practices into their curriculum. Medical students, as well as pharmacy and nursing students among others, are studying the use of complementary therapies along with conventional therapies in their clinical case studies as part of educating the next generation of physicians and other health professionals.

Research

What we really want to know as clinicians and investigators is whether there is clinical effectiveness of a complementary therapy and if there is, what is the mechanism of action? The NCI and the NCCAM are now funding pilot studies and well-designed randomized trials of CAM therapies.[1,13] Through 2005, NIH budget allocations for IM research have increased substantially. NCI's OCCAM office is set up to hear testimonials from CAM practitioners and to determine whether there is enough data to warrant further study and an RFA. CAM practitioners are asked to submit their clinical data, pathology slides, treatment and outcome data to OCCAM for review. As Dr. Stephen Straus, Director of NCCAM, reminds us, "the plural of anecdote is not evidence." At institutions like Dana-Farber Cancer Institute, pilot studies have been carried out to determine feasibility of performing clinical research on IM. It would then be expected, based on the pilot studies, that well-designed, randomized, placebo-controlled studies (RCTs) would follow. Doing RCTs in CAM requires that CAM practitioners acquire new expertise. Recently, we studied the feasibility of performing acupuncture in patients with advanced cancer and its effect on pain, nausea and the qual-

Table 1. Drug-herb interactions.

Herb	Drug	Effect
Echinacea	Cyclophosphamide Vinca alkaloids	CYP3A4 induction
Essiac	Anthraquinones Others	Inhibition of CYP3A causes synergism with chemotherapy
Garlic	Warfarin	Interaction, decreased effect
Ginkgo	Cyclophosphamide Vinca alkaloids	CYP3A4 & CYP2C19 inhibition
Ginseng	Cyclophosphamide	CYP3A4 inhibition
Milk thistle	Doxorubicin	Inhibition of P450 thus decreasing metabolism of doxorubicin
St. John's wort	Cyclosporin Ironotecan Taxanes Imatinib	Subtherapeutic levels of chemotherapeutic agents metabolized by CYP3A4

Table modified after reference 17

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ity of life.[43] The first aim was to determine whether enough patients with advanced stage disease could come into an urban ambulatory setting for 8 weeks of acupuncture (twice a week for 4 weeks, then once a week for 4 weeks), followed by two additional questionnaires within 4 weeks after completion of the acupuncture, for a total study period of 12 weeks. The second aim was to determine whether the quality of life tools could detect changes in symptoms and other aspects of life quality and satisfaction. Forty patients with advanced breast and ovarian cancer entered the study and 28 (70%) completed 4 weeks of the study while 26 (65%) completed the entire study, which met the feasibility criteria. Fourteen (35%) withdrew, 8 before receiving any acupuncture and 6 during active treatment. The study proved feasible and outcomes suggested positive trends of improvement in fatigue, pain severity and interference, anxiety, depression and insomnia. Enough information is available to warrant a randomized clinical trial with a control arm. The control arm for such a study should account for the placebo effect. "Sham acupuncture" is one example of such a control arm, but needs to be carried out with proper masking, enrolling study patients who either have not had any prior acupuncture treatments or no recent acupuncture experience. This, however, raises the ethical issue of conducting a clinical trial with a placebo arm in end-stage cancer patients; many IRBs currently list such patients as "at risk" populations and will not allow trials without potential benefit to the participating patients.

Summary

As clinical researchers in academic hematology/oncology centers, what have we learned about this evolving field? Clinicians need to ask about their patients' CAM use. There needs to be attention to patients' quality of life issues, symptom management and lifestyle while they are undergoing conventional therapies. Finally, the research agenda must include well-designed trials of CAM or integrative therapies to determine those that can become evidence-based by either impact on survival, reduction in symptoms and/or improved well-being and quality of life.

Future Directions

A new society was formed to address scientifically the many questions raised. The Society for Integrative Oncology (SIO) is an international organization of oncology professionals studying and integrating effective complementary therapies in cancer care. Although IM is in its infancy, the first international conference of the SIO, held in November 2004, included over 600 participants from 4 continents. The goal of the conference was to "educate oncology pro-

Table 2. Examples of clinical research studies in integrative medicine (IM).

Complementary Therapy	Phase Trial	No. of Pts.	Outcome	Refs
Acupuncture for:				
1. Chemotherapy-induced nausea and vomiting	6 RCTs	739	Reduced severity and duration of nausea and number of bouts of vomiting	26
2. Cancer pain	RCT	90	Decrease in pain intensity by visual analog scale	34
3. Post-chemotherapy fatigue	Pilot	37	Mean improvement in baseline fatigue score	33
Massage therapy for:				
1. Anxiety, stress	RCT	34	Immediate effect post massage in distress as measured by State-Trait Anxiety Inventory (STAI)	32
2. Nausea in autologous marrow transplant	RCT	34	Immediate effect post massage as measured by STAI	32
Antioxidant:				
Childhood acute lymphocytic leukemia (ALL)	Observational study	103	Greater Vitamin C intake associated with fewer therapy delays, less toxicity, and fewer hospital days Greater Vitamin E intake associated with lower incidence of infection Greater Beta-carotene intake associated with decreased risk of toxicity Lower intakes of antioxidants associated with increase in adverse side effects of chemotherapy	44
Antioxidant in conjunction with radiation therapy	Review	NA*	Reactive oxygen species (ROS) have been implicated in the onset and development of the disease. Experimental studies show that antioxidants that prevent ROS damage can act as cancer protective agents. Once cancer has developed, radiation therapy relies on ROS toxicity to eradicate tumor cells, thus raising questions about the simultaneous use of antioxidants and radiation.	17
Relaxation training and guided imagery during chemotherapy	RCT	96	Patients in experimental group were more relaxed and easy going during the study. Quality of life was better. Imagery ratings correlated with clinical response.	45

* In-vitro study
Abbreviations: RCT, randomized placebo-controlled study

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fessionals and other health care stakeholders about state of the art integrative therapies." The conference addressed the data behind complementary therapies and their efficacy in oncology practice, essentially emphasizing evidence-based practices. Attendees at the conference learned about important work that is being done internationally in developing Integrative Cancer Centers. Plenary sessions and research studies covered areas such as acupuncture for cancer symptoms, as well as the use of botanicals, phytoestrogens and antioxidants in the treatment of cancer. Participants also learned about the importance of phase I and II trials of CAM therapies (**Table 2**) and how to navigate the Investigational New Drug (IND) submissions of these agents to the FDA. Although models of integrative medicine in disciplines other than oncology are being formulated, "integrative oncology" may serve as a model for other specialties.

The SIO can serve as a forum for the presentation of scientific data on complementary therapies, while emphasizing the importance of developing an infrastructure that promotes the principles and practices of IM. The ultimate goal is to develop multi-disciplinary expertise, as well as therapeutic synergy, between conventional and complementary therapies.

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