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Primer on Integrative Oncology

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Integrative medicine, often called complementary and alternative medicine (CAM), is the use of non-Western medicine as part or all of the treatment of disease. The use of such nonstandard approaches is particularly prevalent in oncology [1–4]. Patient preference for such medicine may represent their dissatisfaction with standard medicine [5,6], an alternative after the failure of standard therapy [7], or patient personality factors [8,9].

There is no definition of a "standard" or an "alternative" approach. For example, although the use of high-dose vitamin A would be considered "alternative" by most studies surveying the use of alternative medicine, the use of a vitamin A analogue, such as retinoic acid, would not. Similarly, the use of aloe vera extract would be considered a part of alternative medicine, but the use of commercial aloe-based products would not. Prayer is also considered an alternative therapy, although many patients would consider it a part of their everyday life, rather than nontraditional care [10].

The National Center for Complementary and Alternative Medicine separates alternative medicine techniques into five areas (Table 1) [11]. The following sections review current research in these areas, with emphasis on randomized trials relevant to the treatment of cancer. The challenges facing research into integrative oncology are also summarized.

BIOLOGICALLY BASED PRACTICES

What Is a Dietary Supplement?

The most common CAM approach used by patients in the United States is the use of dietary supplements [12]. The term "dietary supplements" is important, because the US Food and Drug Administration (FDA) does not prospectively regulate the efficacy of dietary supplements [13]. A dietary supplement may include "vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites" [14]. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, dietary

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Table 1
Major areas of complementary and alternative medicine

Major area of CAM	Examples
Biologically based practices	Dietary supplements, herbs
Energy medicine	Healing touch, Reiki, prayer
Manipulative and body-based practices	Massage therapy, chiropractic, reflexology
Mind-body medicine	Hypnosis, qi-gong
Whole medical systems	Traditional Chinese medicine, Ayurvedic medicine, homeopathy

From National Center for Complementary and Alternative Medicine. Health information. Available at: http://nccam.nih.gov/health.

supplements were reclassified as neither foods nor drugs. The manufacturer of the dietary supplement is required to demonstrate that the supplement is safe and that claims of efficacy are supported by evidence, but the manufacturer is not required to submit this information to the FDA. A new dietary supplement (one not available before the enactment of DSHEA) is required to undergo a premarketing review for safety data but not for efficacy. A dietary supplement must also carry the statement that "a dietary supplement is not intended to 'diagnose, treat, cure or prevent any disease,' because only a drug can legally make such a claim" [15]. The dietary supplements can make statements about structure and function ("calcium builds strong bones"), and specific disease treatment claims can be made, if approved by the FDA (eg, "25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease") [16]. Dietary supplements can also make a claim that "describes general well-being from consumption of a nutrient or dietary ingredient" [13]. For example, the statement that St. John's Wort helps maintain a balanced lifestyle is within the FDA guidelines, but a statement that St. John's Wort can treat mild-to-moderate depression would reclassify it as a drug and require FDA approval for marketing.

Vitamins and Single Agents

Vitamin C

Vitamins and single agents, such as melatonin, are increasingly used by the general public and patients who have cancer [17]. Much early work focused on vitamin C, sparked by Linus Pauling's enthusiasm for vitamin C and by data from other centers [18–20]. Cameron and Pauling [18,19] administered high-dose vitamin C (10 g/d intravenously for 10 days followed by oral supplementation) to 100 patients and compared the survival "from the date of untreatability" of the cancer of these patients with 1000 similar control patients. The date of untreatability was determined by a review of the patient's charts and a designation of the patient's "untreatability by such conventional standards as the establishment of inoperability at laparotomy, the abandonment of any definitive form of anti-cancer treatment, or the final date of admission for 'terminal care.' This presentation date of untreatability corresponds to the date when ascorbate

supplementation was initiated in the treated group" [18]. Cameron and Pauling [19] found that the slope of the mortality curve of the treated patients was one third that of the historical controls. The same authors then reproduced these results against another set of historical controls. A Japanese group presented similar data [20].

In contrast to these findings, Moertel and colleagues [21,22] at the Mayo Clinic published two randomized trials of oral vitamin C supplementation in patients who had advanced cancer and found no survival advantage. In these trials (which enrolled 123 and 100 patients, respectively), there was no survival advantage to supplementation with 10 g of oral vitamin C. Pathak [23] recently published the results of a trial of oral supplementation with ascorbic acid (vitamin C, 6100 mg/d), DL-alpha-tocopherol (one form of vitamin E, 1050 mg/d), and beta-carotene (vitamin A precursor, 60 mg/d). Patients who had stage IIIB or IV non–small cell lung cancer were randomly assigned to treatment with chemotherapy (paclitaxel and carboplatin, 72 patients) or to the chemotherapy regimen plus the supplements (64 patients). No significant survival differences were reported, with 1-year survival rates of 33% and 39% and 2-year survival rates of 11% and 16% in the chemotherapy and the combination arms, respectively. It may be argued that the inability to confirm Pauling's [24] results can reflect the use of oral rather than intravenous vitamin C. A 1.25-g dose of vitamin C given orally results in a mean plasma level of 135 μmol/L, whereas the same dose given intravenously results in a level of 885 μmol/L. The same study showed that the maximum tolerated oral dose of 3 g every 4 hours increased the plasma level to only 220 μmol/L, whereas the maximum tolerated intravenous dose of 50 g resulted in a plasma level of 13,000 μmol/L. The form of oral vitamin C also affects its bioavailability. A solution of vitamin C has an approximately 40% lower bioavailability than a slow-release formula [25].

Vitamin C intake has also been examined for the amelioration of toxicity associated with chemotherapy administration. Weijl and colleagues [26] investigated the use of oral vitamin C, vitamin E, and selenium for the prevention of cisplatin-induced renal toxicity and ototoxicity. No significant overall effect was demonstrated, but there was a correlation with plasma levels of the vitamins and lower toxicity. The authors concluded that poor compliance or inadequate supplementation may have confounded the results.

Vitamin A and vitamin E

The other extensively studied vitamins are vitamin A (and vitamin A analogues) and vitamin E compounds. The Beta-Carotene and Retinol Efficacy Trial enrolled 18,314 patients who were randomly assigned to receive placebo or daily beta-carotene (20 mg) and retinyl palmitate (25,000 IU) [27]. The trial was stopped early because the patients receiving the supplement had a 28% increase in lung cancer incidence and a higher risk of death from lung cancer than did the controls. This increased risk persisted after the stopping of the supplementation. Similarly, the Alpha-Tocopherol Beta Carotene Prevention Study was a study of 29,133 male smokers who were randomly assigned to receive alpha-

tocopherol alone (50 mg/d), beta-carotene alone (20 mg/d), both compounds, or placebo [28]. They found no effect from alpha-tocopherol alone, but there was an 18% increase in the incidence of lung cancer among men in the two arms who received beta-carotene and a 46% higher death rate from lung cancer among patients who received beta-carotene [29]. A randomized trial of beta-carotene (50 mg every other day) among 22,071 physicians, however, showed no negative effects from the supplementation, even among current and former smokers [30]. Bairati [31] published findings of a double-blinded, placebo-controlled trial of 3 years of alpha-tocopherol (400 IU/d) and beta-carotene (30 mg/d) for the prevention of second cancers among 540 men who had a history of head and neck cancer. The beta-carotene supplementation was discontinued after 156 patients because of ethical concerns raised by these trials. There was no overall change in the risk of second cancers, but the risk of recurrence or second cancer was higher during supplementation (2.88 for alpha-tocopherol alone and 1.86 for the combined group) and decreased after supplementation was stopped. The patients receiving the supplement did have a lower rate of radiation-related acute toxicity [32]. This ability of vitamin E to reduce radiation mucositis was also shown in a randomized trial of an oral rinse. Patients rinsed during radiotherapy with vitamin E oil or with the carrier oils before radiation and 8 hours later. Fifty-four patients were randomly assigned, and the risk of symptomatic mucositis was reduced from 33% to 22% (P=.038) [33].

Zinc

A placebo-controlled, randomized study of zinc supplementation (45 mg/d orally) during radiotherapy that enrolled 18 patients showed that patients receiving placebo had a greater loss of taste acuity and a slower return of taste acuity than did patients supplemented with the zinc [34]. Another placebo-controlled, randomized trial of 27 patients showed that 50 mg of oral zinc sulfate taken during radiation therapy reduced the risk of severe mucositis and delayed the onset of mucositis [35].

Melatonin

Melatonin has been studied both as a primary treatment and as a supportive agent [36,37]. Most trials, however, have been from a single group, Lissoni and colleagues in Italy. They demonstrated a significant survival advantage with the use of nightly melatonin for patients who had advanced colorectal cancer [38], advanced solid tumors [39], cisplatin-resistant metastatic non–small cell lung cancer [40], brain metastases [41], relapsed melanoma [42], and glioblastoma multiforme [43]. They have also shown quality-of-life advantages for melatonin for patients receiving chemotherapy [39,44–47]. Three trials performed by other centers have failed to show any survival advantage [48,49] or reduction in toxicity [48,50] with melatonin, however. For example, the Radiation Therapy Oncology Group 0119 trial found the addition of melatonin to standard palliative radiotherapy had no survival advantage over radiotherapy alone for patients who had brain metastases [49].

Hydrazine sulfate

Gold [51] first proposed the use of hydrazine sulfate for the treatment of cancer based on a model of cancer cells having altered glucose use. Three subsequent randomized trials in patients who had cancer failed to demonstrate any improvement in survival and perhaps showed a decrease in survival for patients receiving hydrazine [52–54]. A randomized trial of patients who had cachexia secondary to cancer did, however, show improved maintenance of weight with the use of hydrazine [55].

Herbal Preparations

Mistletoe extracts

The most extensively studied herbal preparation is mistletoe, which has been studied as both a naturopathic (standard-dosing) and homeopathic (high-dilution) compound. The studies do not always clearly indicate which type of mistletoe preparation was used. The two most commonly studied compounds are Iscador and Helixor. Mistletoe is exempt from FDA regulation in the United States when used as a homeopathic compound. Any compound sold and used as described in the Homeopathic Pharmacopoeia of the United States can be sold without FDA approval [56], but no compound, including homeopathic compounds, can be given intravenously without prior FDA approval. Therefore intravenous mistletoe extracts cannot be legally administered in the United States except under an investigational new-drug license from the FDA. The approval of mistletoe extracts for use in other countries generally reflects the differences in the regulatory environments. In the United States, a drug is approved if it is proven to be efficacious. In other countries, such as Germany, a drug is approved for use if it is proven to be safe. Ernst [57] reviewed the randomized clinical trials of mistletoe for treatment of cancer. Placebo-controlled phase III trials performed with standard research techniques have been reported for melanoma and head and neck cancer. The head and neck cancer trial randomly assigned 477 patients after surgery or after surgery and radiotherapy to receive a mistletoe extract (Eurixor) twice weekly for 60 weeks [58]. There was no difference in disease-free survival or quality of life. The melanoma trial was run within a larger European Organization for the Research and Treatment of Cancer (EORTC) trial of interferon for high-risk patients [59]. The primary randomization was between gamma-interferon, alpha-interferon, and a non-treated control group. The German Cancer Society added a fourth arm that received Iscador-M. The results are reported for 423 patients in the EORTC trial and for 407 patients in the German subtrial [59]. At a median follow-up of 8.2 years, the mistletoe extract had no effect on overall survival or disease-free survival. There was a trend for poorer survival for the Iscador-M arm. Two small, randomized studies of Iscador, one for breast cancer with axillary metastases and the second for other cancers, showed significant survival advantage for the use of Iscador [60]. In contrast, a 60-patient randomized, phase II trial of subcutaneous mistletoe extract versus no treatment for superficial bladder cancer showed no difference in recurrence and progression between the two arms [61].

Extract of Greater Celandine sterols

One herbal product with encouraging phase III results is an extract of the sterols of the European plant Greater Celandine. Two randomized trials have been reported. In the first, 42 patients who had locally advanced or metastatic pancreatic cancer and who had refused standard chemotherapy were randomly assigned to treatment with high-dose vitamin C and celandine extract or vitamin C alone [62]. The vitamin C–only arm had a 1-year survival rate of 14%, and the celandine extract arm had a 1-year survival rate of 81%. The median survivals were 9 and 22 months, respectively. A second trial was reported from Ulm, Germany. In this trial, 100 patients who had locally advanced or metastatic pancreatic cancer were randomly assigned to treatment with gemcitabine (standard Burris protocol), celandine extract, or gemcitabine and celandine extract. The median survivals were 5.2 months, 7.9 months, and 10.4 months, respectively ($P = .01$ for gemcitabine versus gemcitabine plus celandine extract). Unfortunately, there have been no further reports on this compound [63].

Ginger

Several studies have demonstrated the efficacy of ginger for the treatment of nausea and vomiting. Most of the investigations involved pregnant women [64–68]. A randomized study of ginger for the amelioration of nausea caused by platinum-based chemotherapy showed that ginger is at least equivalent to the commonly used medication metoclopiramide and has less toxicity [69].

Amygdalin

Amygdalin is an extract of apricots. It is metabolized to cyanide and can be lethal. Amygdalin was recognized as being too toxic for human use, and therefore Ernest Krebs, Jr. synthesized a less toxic form, which he called amygdalin. This compound is often called vitamin B_{17}, although there is no known physiologic need for amygdalin that would qualify it as a vitamin. In a clinical trial of 127 patients who had cancer, there was no reported advantage of the detoxified form of amygdalin in survival or quality of life [70].

Other Compounds

A seemingly infinite number of other alternative compounds and treatment techniques are offered to patients who have cancer. Among the most widely used are antineoplastons [71], enzyme preparations [72], and oxygenated water (vitamin O) [73]. No rigorous clinical trial data have been reported for these compounds.

Discussion

Few complementary and alternative compounds have been adequately tested with randomized phase III clinical trials to show efficacy for either the treatment of cancer or for the reduction of the toxicities associated with cancer and its treatment. Therefore, until such agents have been properly tested, they

cannot be recommended for routine use by oncology patients. Agents that appear from the available evidence to be appropriate for use include ginger, zinc, and perhaps short interventions with moderate-dose vitamin E. In contrast, there is insufficient clinical evidence to warrant the use of melatonin and mistletoe outside of clinical trials. Celandine extract has shown encouraging efficacy for patients who have pancreatic cancer and should be studied further in larger randomized trials.

ENERGY METHODS

There are many energy methods available as complementary treatments for patients who have cancer. The most commonly used in the United States include healing touch [74], therapeutic touch [75], and Reiki therapy [76]. All these approaches attempt to correct the energy flows through the patient, generally by using the energy of the practitioner to supplement or correct the patient's disturbed flows. They are primarily used for improvement of the quality of life of patients who have cancer rather than as a direct treatment of the cancer. Acupuncture can also be considered an energy method, but it is discussed in the section on traditional Chinese medicine (TCM).

Studies

There have been no randomized studies of energy techniques as primary treatment for cancer. There have, however, been at least two randomized trials of healing touch as supportive care for patients who have cancer. In the first, patients undergoing chemotherapy were randomly assigned to one of three arms. Patients in one arm received both healing touch and massage; the second arm was treated with presence (a person was near the patient but did not interact). The third arm received standard care. After 3 weeks, the patients were crossed over to the other arms. The authors found that massage therapy and healing touch were more effective than presence or standard care for the reduction of pain, mood disturbance, and fatigue [77]. The trial design does not preclude the possible bias of a placebo effect. A second trial studied healing touch during radiation therapy. Patients were randomly assigned to receive healing touch or mock treatment [78]. The mock therapy was given by untrained individuals who rotated around the patient as if treating but did not attempt to give therapy. One potential bias in this study was that the trial was offered to 224 patients, but only 78 agreed to participate, and only 62 were included in the final analysis. The authors state that the active intervention significantly improved the patient's quality of life as measured by a validated health status survey, the Medical Outcomes Study Short Form Health Survey (SF-36) [79]. Review of their data, however, suggests that the initial imbalances in the distribution of the patients' characteristics may have accounted for the differences in outcome.

Prayer can be considered an energy technique. Testing in this area is obviously difficult, because personal beliefs can affect subjective measures of out-

come. Remote intercessory prayer (distance prayer) removes this bias. In distance prayer, people who are unknown to the patient pray for the patient. The patients do not know whether they are prayed for [80–85]. A controversial study showed efficacy for prayer for patients in a coronary care unit [83], undergoing in vitro fertilization [86], and treated for bloodstream infection [85]. The most recent and largest study examining intercessory prayer did not show any effect for patients undergoing interventional cardiac care [87]. This study also found no advantage to bedside combined music, imagery, and touch therapy. No randomized studies in cancer have been reported. A Cochrane review on intercessory prayer as a treatment found insufficient data to reach a positive conclusion [82].

Discussion

There are insufficient clinical trial data to confirm that energy methods improve the quality of life of patients who have cancer, and no evidence-based data suggest that energy methods improve the survival of these patients. Given the benign nature of these interventions, and the possibility of a positive placebo effect, there is no obvious reason to discourage their use.

MANIPULATIVE AND BODY-BASED METHODS

The manipulative methods most commonly used as an integrative treatment approach are chiropractic and osteopathic manipulation, massage therapy, and reflexology. Chiropractic and osteopathic manipulations are designed to realign the vertebral bodies, spinal cord, and nerves to correct energy imbalances. Massage therapy is muscle manipulation as administered by trained therapists. Various massage methods can be used (eg, Swedish, deep tissue, and shiatsu) [88]. Reflexology is the use of pressure on specific points on the foot to relieve systemic symptoms [89].

Studies

A PubMed search found no randomized trials of osteopathic or chiropractic manipulation for patients who have cancer. In 2000, a Cochrane review of massage therapy and aromatherapy plus massage therapy for patients who had cancer found insufficient evidence to reach a conclusion on efficacy [90]. A recent review further updates these findings and reviews the safety of massage therapy [91]. This review suggests that massage therapy may be effective for stress reduction. Risks of massage therapy among patients who have cancer include bleeding in patients who have a coagulation disorder and fracture in patients who have bone metastases.

Yang [92] reported on a randomized trial on reflexology for patients who have cancer. This article is in Korean, and only the abstract was available in English. From the abstract, 34 patients undergoing chemotherapy were randomly assigned to reflexology or to a control group. The authors reported a decrease with reflexology treatment in cancer-related nausea and in fatigue.

Discussion

There are insufficient data to determine the efficacy of manipulative therapies. There are risks from massage therapy to susceptible patients. As discussed later, traditionally designed randomized trials of manipulative therapies may be impossible. Massage therapy should not represent a significant risk and may be offered to patients who have cancer except for those who have conditions such as an increased risk of bleeding or bone metastases. Similarly, there is little risk from reflexology, although its efficacy is unproven. The role of other manipulative techniques, such as chiropractic and osteopathy, are unknown.

MIND–BODY MEDICINE

Mind–body Techniques

There are a host of mind-body alternative techniques. The most studied mind–body technique is hypnosis. Relaxation and guided imagery are closely related to hypnosis. Yoga and qigong can also be considered as mind–body techniques.

Clinical Trials

Hypnosis

Hypnosis is the process of placing a person in a relaxed state either to implant suggestions or to determine root causes of problems by releasing inhibitions or improving memory. There is some debate, even among practitioners, whether hypnosis differs significantly from a relaxed state [93,94]. Hypnosis is a technique that can be studied within the setting of a randomized trial, usually by having a control group that is hypnotized or undergoes deep relaxation without suggestions.

Stalpers [95] reported on a randomized trial of hypnotherapy for patients who had cancer and were undergoing radiation therapy. The trial did not use sham hypnosis as a control intervention. Among the 81 patients randomly assigned to hypnosis or no hypnosis during radiation therapy, there were no differences in anxiety, as measured by the State-Trait Anxiety Inventory, or on the SF-36 health status survey. The patients receiving hypnotherapy recounted a subjective improvement in their well being, however. In an earlier randomized trial of 50 terminally ill patients who had cancer, half of the patients had standard care supplemented with four weekly sessions with a hypnotherapist [96]. The patients undergoing hypnotherapy had a significantly better quality of life (as measured by the Rotterdam Symptom Checklist) and less anxiety and depression (as measured by the Hospital Anxiety and Depression Scale). Again, there was no sham hypnosis in the control arm to reduce the risk of the placebo effect. Rajaseskaran [97] recently reviewed the use of hypnotherapy for patients who had advanced cancer and concluded there were insufficient data to reach a conclusion on the efficacy of hypnotherapy for these patients.

Qigong, yoga, and meditation

Qigong and yoga both use body movements to improve the energy flows within the body. Qigong aims to correct the flow of qi, the basic energy in TCM,

whereas yoga orients the flow through the chakras and is derived from traditional Indian medicine (Ayurvedic). Many trials have been run on these two approaches among patients who have cancer, generally to relieve symptoms. It is difficult to design an appropriate control group to separate out the placebo effect, however. In one randomized study of Tibetan yoga, 39 patients who had lymphoma and were undergoing treatment or had completed treatment within the previous 12 months were randomly assigned to yoga sessions or to a waiting list [98]. Multiple assessments were performed, including distress using the Impact of Events Scale, anxiety using the Speilberger State Anxiety Inventory, depression using the Centers for Epidemiologic Studies–Depression, fatigue using the Brief Fatigue Inventory, and sleep disturbances using the Pittsburgh Sleep Quality Index. Only the sleep-quality index showed any difference between the two arms, with the yoga group having improved sleep. A similar study, with the same treatment–wait-list design, used a mindfulness meditation-based stress reduction program [99,100]. Patients were followed using the Profile of Moods Scale and the Symptoms of Stress Inventory. The active arm showed less mood disturbance and less anxiety, and these effects continued to be seen at 6-month follow-up.

Discussion

Few randomized mind–body intervention studies have been completed, perhaps because of the difficulty of using the placebo-controlled, double-blinded model in this situation. The studies reviewed cannot exclude placebo effect as the basis for their results. Therefore no evidence-based conclusion can be reached on the efficacy of these interventions. Given the low level of risk with these techniques when given by trained personnel, there is no obvious reason to restrict patient access to such therapies. The patient and practitioner should be open about the lack of supporting data.

WHOLE MEDICAL SYSTEMS

The modern Western medical tradition rests on the principles of Newtonian physics and reductionism [101]. In this view, the body is made up of a series of parts, and these parts can be evaluated independently of the whole. Therefore disease is seen as a failure of some part of the body, or invasion by something external to the body. Most alternative medical systems view the body as a complex whole. Health occurs when all of the parts of the body are functioning normally, and the goal of medicine is to restore the body as a whole to its normal balance [102]. The three most common alternative systems practiced in the United States are homeopathy, TCM, and Ayurvedic medicine from the Hindu tradition. TCM and Ayurvedic medicine share many traditions, and in both the goal is to restore the normal energy flows of the patient to balance. These systems are highly developed and cannot be summarized here (see Berk [102]). Certain parts of TCM are used in the West, such as acupuncture, and the research on these areas is reviewed.

Health in TCM can be simplistically presented as the balance of qi in the organ systems of TCM anatomy. The qi flows through the body along channels or meridians. The location of these meridians is fixed. Techniques such as acupuncture and moxibustion (the burning of moxa at specific sites along the meridians) are used to enhance the flow of qi when it has been disrupted by internal or external agents. The TCM physician evaluates the patient based on symptoms and signs. The signs include the color and texture of the tongue, the pulse, and the color of the patient's skin. Treatments, including herbal preparations and acupuncture, are then applied to treat the patient [102].

Similarly, health in Ayurvedic medicine is the balance of the energies of the body. The internal energy is Prana, and health is the balance of Prana and the material forces (doshas), Vata, Pitta, and Kapha. These three are somewhat analogous to the humours of Galenic medicine. To restore health in a diseased body, various purification rituals are used, such as purging and enemas. Also diet and herbs are employed to rebalance the doshas and regain health [102].

Homeopathy is a European tradition, although it is now widely used in India. It is also based on a holistic approach to patient care. Homeopathy has diverged somewhat and is practiced as classical homeopathy and modern homeopathy. In either approach, disease is a manifestation of a single, deep illness and represents a physical manifestation of a few universal diseases and their psychologic overlays. The goal is to cure the underlying disease. In classical homeopathy the disease should be curable by a single agent. In contrast, modern homeopathy often uses mixtures of agents. Most people are more familiar with homeopathy as the use of infinitely dilute medications as treatment. This theory is based on the supposition that a symptom is induced by a full concentration of a compound will be cured by the compound if it is infinitely diluted and shaken [102]. Thus a compound that induces nausea at full strength will cure nausea if it is diluted a billion-fold. This treatment is only one part of the complete homeopathic system. As in standard Western medicine, the homeopathic system is based on the ability to diagnose a patient's underlying illness and present symptoms so as to choose the appropriate cure. The illnesses and cures, however, are specific to the homeopathic system.

Clinical Trials

Traditional Chinese medicine

Most randomized trials of TCM have been done with acupuncture, but most acupuncture as practiced by Western physicians is not related to TCM. Rather, it is based on a French system developed in the mid-1900s. The primary difference is that in TCM each patient is analyzed for the underlying disease, and acupuncture sites are chosen based on the underlying disease. In the French system, specific acupuncture sites are correlated with specific symptoms, and all patients with that symptom receive the same treatment. For example, in the French system nausea is treated at specific acupuncture sites. In TCM, nausea is one part of a diagnostic paradigm; depending on other signs and symptoms, an energy imbalance would be seen, and acupuncture sites would

be chosen according to this imbalance. This latter approach is not compatible with randomized trials, however, so the French approach is most often used in clinical trials. For example, a specific acupuncture point, rather than a site based on the overall condition of the patient, is used for all patients in a Western trial of acupuncture for the treatment of nausea.

There have been several trials of acupuncture or acupuncture-like treatments for nausea in patients who have cancer. Roscoe [102] tested acustimulation (slight electrical stimulation delivered by a band to an acupuncture point) [103]. No specific acupuncture point was targeted. The trial randomly assigned 731 patients receiving chemotherapy to either the active band or no band. There was a statistically significant reduction in nausea among men and a strong trend among women ($P = .052$). Smaller studies by Triesh [104] and by Pearl [105] also showed possible efficacy of acustimulation, whereas a trial by Ozgur [106] was negative. Shen [107] randomly assigned 104 women receiving chemotherapy for breast cancer to one of three treatments: antiemetics and electroacupuncture at what are considered active antinausea acupuncture sites, antiemetics and sham acupuncture at inactive acupuncture sites, or antiemetics only. The active treatment decreased nausea over the first 5 days of chemotherapy but not over the next 10 days. Similarly, Noga [108] investigated the effect of acupressure (pressure at acupuncture points). In this study 107 patients were randomly assigned to the use of acupressure bands on the P6 point or at an inactive point. The acupressure group had higher nausea levels than the control group ($P < .001$). This trial was presented only in abstract form.

Other trials on acupuncture for patients who have cancer are more limited. Blom [109] reported on a randomized trial of acupuncture for radiation-induced xerostomia and found no difference between active and sham acupuncture among 38 patients. Prospective, nonrandomized trials have shown some efficacy for cancer-related breathlessness [110], male hot flashes caused by castration [111], and female hot flashes caused by tamoxifen [112].

Ayurvedic medicine

The only randomized trial of an Ayurvedic medicine for patients who have cancer was for the prevention of morphine-induced constipation. Patients were randomly assigned to the use of a standard stool softener or an Ayurvedic preparation [113]. There was a nonsignificant decrease in constipation among the Ayurvedic patients.

Homeopathy

Several studies have been performed on homeopathic preparations for the supportive care of patients who have cancer. Balzarini and colleagues [114] reported on the use of a homeopathic mixture to reduce skin reaction during radiation therapy. The authors report that the homeopathic mixture prevented skin reaction, but the design and analysis of the trial is unclear. Oberbaum [115] reported on a randomized trial of a homeopathic mouth rinse

(Traumeel) for the prevention of mucositis during pediatric bone marrow transplants. Thirty-two patients were enrolled. There was significantly less mucositis in the Traumeel arm.

Discussion

There are no controlled, clinical trials showing that an alternative medical system is an effective treatment for cancer. Several trials suggest that parts of alternative medical systems, such as acupuncture and homeopathic drugs, may be active. Much more research is needed before any recommendations for the use of alternative systems or their components can be given. The use of alternative herbal preparations, such as Chinese herbs, should be a cause of great concern. Many imported herbal products are adulterated and may contain dangerous contaminants [116,117]. Also, herbal products may cause significant toxicity as well as interact with other medications [118,119].

RESEARCH AND INTEGRATIVE ONCOLOGY

Research in integrative oncology is complex. Some of the problems associated with CAM trial design were reviewed recently by Buchanan and colleagues [120] from the US National Cancer Institute. Simple products, such as vitamins, and compounds, such as melatonin, can be tested in standard, placebo-controlled trials, but trials with herbal products, such as ginseng or St. John's Wort, are much more difficult. The first issue is to define the appropriate form of the herb and to define a quality assurance program. Natural products are highly variable, and one batch may differ significantly from another. Natural products are also sensitive to aging, so quality control must be continuously performed even on a single batch. Then caution must be taken to minimize the risk of natural product–drug interactions. For example, a national trial of St. John's Wort was recently closed because of poor accrual and major concerns over drug–herb interactions (Edward Shaw, personal communication, 2005).

Outside of alternative therapies that can be tested against a simple placebo control, the trials become even harder to design. Alternative medical systems do not define diseases using the same paradigm as Western medicine. Therefore patients cannot be randomized between Western treatment and an alternative medical system. Further, a single-treatment approach may not be appropriate for all patients who have the same disease, depending on the constitution of the patient. Therefore a standard alternative treatment cannot be defined. Mind–body and energy treatments represent challenges primarily in the difficulty in defining a placebo control arm. Most of these studies are for supportive care and therefore have subjective endpoints (eg, pain, nausea). Without appropriate blinding and placebo arms, efficacy may reflect only the placebo effect.

Another problem in research in alternative medicine is that many practitioners of alternative medicine do not subscribe to the same standards of proof as Western researchers [121,122]. They may believe that millennia of use or the absence of harm justify their methods beyond the need for randomized, controlled trials. Therefore they refuse to participate in clinical trials.

SUMMARY

At the present time, there is no obvious answer for many of these design difficulties. This problem will continue to constrain ability to determine the efficacy of integrative medical techniques for patients who have cancer. Patients, however, will continue to gravitate toward alternative treatments, especially when standard cancer treatments fail. Therefore oncologists must be aware of alternative medical agents and techniques, and be able to guide their patients, rather than simply being dismissive.

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