Clinical Trials in Cancer Part II

Biomedical, Complementary, and Alternative Medicine: Significant Issues

CDR Colleen O. Lee, RN, MS, AOCN®

Cancer clinical trials are research studies in humans designed to answer specific questions related to cancer. Meticulously conducted cancer clinical trials are the best method to establish safe and effective preventive, diagnostic, treatment, and supportive care interventions (National Cancer Institute [NCI], 2004). Complementary and alternative medicine (CAM) has become a pervasive component in cancer care, and cancer CAM clinical trials are increasing in number and expanding in design. Oncology nurses are in the forefront of clinical supportive care for patients enrolled in clinical trials. They also are involved in designing clinical trials, accrual, monitoring, data management, analysis, and reporting results. A search for conventional biomedical and CAM clinical trials in the United States was performed. Part I of this article (Lee, 2004) offered a synopsis of how to locate active trials and published results. Part II reviews significant aspects of cancer CAM clinical trials such as accrual, ethical and methodologic considerations, use of CAM in symptom management trials, and the role of nursing in cancer CAM.

Accrual

Accrual of eligible patients into conventional biomedical clinical trials offers continual challenges for the research and practice communities. Multiple and varied viewpoints from patients, oncology nurses and physicians, and researchers with proposed plans for improvement (although without extensive success) have been published. Factors influencing enrollment decisions include perceived benefits, risks, and social benefits of participation; practical considerations (e.g., transportation, day care, time, compensation); availability of interventions outside of the trial; desirability of intervention (or placebo) in the control group; and trust in investigators, research institutions, and study sponsors (Halpern, 2002). When considering the complexity of cancer care in general, three possible patient decisions emerge: (1) the decision to use only conventional approaches, (2) the decision to forgo conventional cancer treatment in favor of alternative therapies, and (3) the decision to combine conventional with complementary approaches for treatment and supportive care.

Patients’ reasons for forgoing conventional cancer treatment were examined in a qualitative study involving 14 cancer survivors (Shumay, Maskarinec, Kakai, & Gotay, 2001). Stated reasons were to avoid bodily harm, a belief that conventional treatment would not make a difference in disease outcome, and a belief that CAM is an effective and less harmful option than conventional cancer care. Verhoef, Hilsden, and O’Beirne (1999) found similar trends as 31 patients with cancer discussed factors in making a decision to refuse some, most, or all conventional treatment. Having a close friend or relative who died when receiving conventional treatment and personal experiences surrounding diagnosis (need for personal control, treatment side effects, and negative physician response when discussing alternative therapies) were main factors in this group.

Accrual of patients into cancer CAM clinical trials appears promising on the surface but may have an added challenge if the trials involve randomization to a conventional care arm. Likewise, patients who desire only conventional treatment may not be amenable to accrual into a trial involving randomization into a CAM plus conventional therapy arm. Conceivably, cancer CAM clinical trials may experience similar accrual barriers as conventional trials, although reporting of these issues in the literature is limited. Richardson, Post-White, Singletary, and Justice (1998) reviewed factors influencing recruitment and reasons for nonparticipation in cancer CAM clinical trials in 158 women with breast cancer who were invited to participate in a study requiring blood samples to assess immune function, emotional well-being, quality of life, social support, and coping strategies. A possible referral to support or imagery sessions was part of the study design. Predictors of participation in this population were age, marital status, and income. Reasons for nonparticipation were...
work and childcare duties, transportation and travel, and lack of interest. Suggestions for increasing accrual were to provide transportation or reimbursement, childcare services, and evening appointments, similar to options offered in clinical trials. Essentially, stimulating accrual in cancer clinical trials is largely uncharted ground, providing the opportunity for novel intervention plans based on viewpoints from patients, nurses and physicians, and researchers.

**Ethical Considerations**

Ethics, a systematic method of answering questions about how and why individuals live and behave (Grady, 2002), is becoming more visible as the availability of CAM treatment and supportive care options increase in cancer care. Oncology nurses, as well as other members of the healthcare team, may engage in conversations with patients who seek knowledge and access to these therapies. Many providers are relatively unfamiliar with CAM therapies, and a lack of consensus exists regarding CAM use along with conventional medicine (Adams, Cohen, Eisenberg, & Jonsen, 2002).

With regard to clinical research in general, comparatively few individuals accept the risk as research subjects to benefit others and society (Grady, 2002). Ethicists raise the point that asking subjects to bear risk of harm for the good of others creates the potential for maltreatment or misuse.

Emanuel, Wendler, and Grady (2000) offered a framework for ethical clinical research composed of seven requirements: social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for subjects. Without social value of the research inquiry, no justifiable reason exists to subject patients to risk in a clinical trial. Furthermore, research must be designed and conducted with rigorous methodology to ensure validity of findings. Studies without social validity are unethical because patients are exposed to risk without the possibility of generalizable knowledge (Miller, Emanuel, Rosenstein, & Straus, 2004).

Ethicists have proposed that CAM research should adhere to the same ethical standards and requirements as conventional research as evidenced in randomized, controlled trials (RCTs) whenever feasible and justifiable ethically (Miller et al., 2004). Rigorous methodology and public input into research focus and prioritization, along with efficacy, must be considered in clinical trials (Jonas, Goertz, Ives, Chez, & Walach, 2004). Clinical decision making should give consideration to (Adams et al., 2002)

- Evidence of safety and efficacy
- Evidence of safety but inconclusive efficacy data
- Evidence of efficacy but inconclusive safety data
- Indication of serious risk or evidence of inefficacy.

Stone (1999) addressed essential ethical issues involving nurses using CAM therapies in clinical practice. Competency to practice CAM therapies follows training courses (with subsequent continuing education) recognized by credible professional organizations offering proof of qualifications and membership. Delivery of CAM therapies usually is not included in a nurse’s scope of practice (unless he or she was hired for this purpose); thus, acquiring and maintaining privileges at the hospital or clinic and state levels is mandatory. Attention must be paid to the informed consent process and documentation of interventions and patient responses. Collaboration with medical practitioners is essential to avoid the possibility of interactions between CAM and conventional interventions (Stone).

Conversations regarding CAM in cancer care stimulate consideration of moral, ethical, and legal obligations of the entire healthcare team. All providers must remain aware of the best available evidence in CAM, presenting evidence in patient-friendly terms and addressing choices from a comprehensive perspective (Cohen, 2001).

**Methodologic Challenges**

Research methodology pertains to how a study is conducted, mainly involving measurement of variables, aspects of control, and statistical analysis (Polit & Hungler, 1991). Much is lacking in the amount of available information for the use of some CAM modalities: numbers and type of patients who use various modalities, how the practices are delivered (e.g., method, dose), how well patients respond, and side-effect profiles (Nahin & Straus, 2001). A common criticism of CAM by conventional biomedical practitioners is the lack of scientifically conducted research. In 2002, an NCI-sponsored expert panel on cancer symptom research identified challenges in CAM research methodology in the following areas (NCI, 2003; Smith, 2004).

- Development of appropriate controls, shams, and placebo interventions
- Development of individualized versus standardized approaches
- Development of new drugs within U.S. Food and Drug Administration regulations
- Ethical issues
- Tools and measurement issues

Major outcomes from the expert panel were the following recommendations.

- Create true controls that will not cause independent beneficial or harmful effects.
- Balance the need for replication in science with the desire to study interventions in a manner that is consistent with clinical practice.
- Obtain investigational new drug status to ensure consistency in product quality and fulfillment of pharmacology and toxicology requirements.

Table 1 summarizes the pervasive methodologic challenges and offers practical solutions.

 Debate continues as to whether the clinical trial design is the optimal avenue for testing cancer CAM treatment modalities or supportive care interventions. As discussed earlier, supporters of the clinical trial design believe that the RCT, which is the “gold standard” in conventional biomedical research, also should be the standard for cancer CAM clinical trials. Although some agree that the RCT is a suitable design for some CAM modalities, others propose the use of both explanatory and pragmatic RCTs (Walker & Anderson, 1999). Pragmatic RCTs do not require that patients or healthcare providers are blind to the modality in use and consider the preferences of patients in the delivery of the modality. Design issues related to the use of a control, methods of assessing effects of individual differences, minimizing therapist variability, determining acceptable inclusion and exclusion criteria, and assessing treatment outcomes are ongoing considerations in pragmatic RCTs (Walker & Anderson). Nonetheless, evidence of effectiveness is critical in the widespread support of the use of conventional as well as CAM interventions and of healthcare providers to administer interventions (Hilsden & Verhoef, 1999). The overall research goal in cancer CAM is to ensure that methodologically rigorous trials are designed and conducted to address the unique challenges without compromising modalities in a manner that is incomplete or inappropriate (Hilsden & Verhoef; Smith, 2004; Walker & Anderson).

**Complementary and Alternative Medicine for Symptom Management**

Symptom management in cancer care spans the prediagnosis to survivorship...
Tremendous advances have been made in offering relief from the minor inconveniences and the major debilitating aspects of symptoms associated with the disease process, its treatment, and the possible physical, emotional, spiritual, and psychological long-term consequences. Conventional approaches to symptom management have been enhanced by the popularity and availability of CAM. Critical appraisal of the quality of CAM in symptom management is available for a limited number of symptoms at this time because of evolving approaches and impending clinical trials. Disease- and treatment-related side effects producing symptoms such as nausea and vomiting, fatigue, insomnia, and mucositis are targeted in clinical trials using CAM approaches for relief, as seen in Table 2.

**The Role of Nursing**

Given the rapidly increasing use of CAM, oncology nurses must become knowledgeable in understanding the role of CAM in cancer care. Oncology curricula in the United States guide nurses to approach cancer care using the principles and practices of conventional biomedical, “Western” medicine. Lack of content, misperceptions, and biases surrounding CAM theory and practice in nursing academic programs can leave nurses essentially unprepared to evaluate CAM clinical care options (Decker & Lee, in press). Nursing curricula without CAM content may inadvertently communicate a lack of validity about the role of CAM in health care and minimize patients’ choice to seek CAM. Once knowledgeable, nurses can begin peer education and establish standards of practice in CAM therapy delivery across practice settings. Nurses must ensure that staff members with proper training deliver CAM therapies and that patients sign informed consent. Medical records must contain documentation of the consent procedures, tolerance, and responses to CAM therapy. Specific endpoints for nursing are offered.

- Expand individual baseline knowledge regarding cancer CAM through verbal and written modes and experiential learning.
- Provide high-quality patient and peer education regarding safety and efficacy of CAM therapies.
- Facilitate partnerships among patients, conventional healthcare providers, CAM providers, and colleagues to discuss knowledge and perspectives about cancer CAM.
- Seek proper training, demonstrate competency, and obtain necessary credentials if practicing CAM.
- Request and require informed consent (with witness) of patients receiving CAM therapies.
- Ensure proper credentialing of CAM providers prior to recommending them to patients.
- Establish institutional-specific standards of practice for the use of CAM therapies in specific patient populations.
- Document patient consent procedures, tolerance, and responses to CAM therapies.
- Design a new integrative care program or assist in the quality maintenance of an established program.
- Develop and update a working knowledge of cost issues and reimbursement of CAM in the community.
- Collaborate in the design of methodologically rigorous cancer CAM treatment and supportive care clinical trials.
- Contribute to the body of nursing knowledge in cancer CAM through publications and presentations in the United States and internationally.
- Develop curricula for undergraduate and graduate nursing schools to examine pertinent topics and stimulate research in CAM.
Table 2. Targeted Symptoms in Cancer Complementary and Alternative Medicine (CAM) Clinical Trials as of April 2004

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CAM Modality Under Study</th>
<th>Name of Protocol</th>
<th>Main Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Acupressure</td>
<td>Phase III randomized study of acupressure for chemotherapy-induced nausea in women with breast cancer receiving one of three combination therapy regimens</td>
<td>MDA-NURO1-396</td>
</tr>
<tr>
<td>Paralytic ileus</td>
<td>Acupuncture</td>
<td>Acupuncture to prevent postoperative bowel paralysis</td>
<td>AT 001065-2</td>
</tr>
<tr>
<td>Chemotherapy-induced nausea and vomiting</td>
<td>Electroacupuncture</td>
<td>Randomized study of electroacupuncture for treatment of delayed chemotherapy-induced nausea and vomiting in patients with newly diagnosed pediatric sarcomas</td>
<td>NCCAM-02-AT-0172</td>
</tr>
<tr>
<td>Symptom distress</td>
<td>Acupuncture</td>
<td>Randomized study of acupuncture to improve end-of-life symptom distress with patients with metastatic colorectal cancer</td>
<td>UPITTS-010901</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Acupuncture</td>
<td>Acupuncture to improve quality of life in patients with advanced cancer</td>
<td>1 R21 AT01010-01</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Acupuncture</td>
<td>Acupuncture for shortness of breath in patients with cancer</td>
<td>1 R21 AT010290-01</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Traumeel® S (Heel Company, Baden-Baden, Germany)</td>
<td>Randomized study of Traumeel® S for the prevention and treatment of mucositis in pediatric patients undergoing hematopoietic stem cell transplantation</td>
<td>COG-ACCL0331</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Massage</td>
<td>Randomized pilot study of massage therapy for the treatment of fatigue in patients with cancer undergoing chemotherapy</td>
<td>OUCSF-H6417-17334-03</td>
</tr>
<tr>
<td>Immunity</td>
<td>Healing touch</td>
<td>Healing touch and immunity in advanced patients with cervical cancer</td>
<td>1 P20 AT00756-01P4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Reiki and energy healing</td>
<td>Reiki/energy healing in prostate cancer</td>
<td>R21AT1120</td>
</tr>
<tr>
<td>Chemotherapy-related nausea</td>
<td>Ginger</td>
<td>Phase II/III randomized study of ginger for chemotherapy-related nausea in patients with cancer</td>
<td>URCC-U1902</td>
</tr>
<tr>
<td>Altered taste</td>
<td>Zinc sulfate</td>
<td>Phase III randomized study of zinc sulfate for the prevention of altered taste in patients with head and neck cancer undergoing radiotherapy</td>
<td>NCCTG-N01C4</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Black cohosh</td>
<td>Phase III randomized study of black cohosh for the management of hot flashes in patients with breast cancer or who have concerns about developing breast cancer</td>
<td>NCCTG-N01CC</td>
</tr>
<tr>
<td>Depression</td>
<td>Hypericum perforatum</td>
<td>Phase III randomized study of sertraline (Zoloft® [sertraline hydrochloride, Pfizer, Inc., New York, NY]) versus hypericum perforatum (St. John's wort) in patients with cancer with mild to moderate depression</td>
<td>CCCWFU-98101</td>
</tr>
<tr>
<td>Sleep</td>
<td>Valeriana</td>
<td>Phase III randomized study of valeriana officinalis (valerian) for improving sleep in patients with cancer receiving adjuvant therapy</td>
<td>NCCTG-N01C5</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Soy</td>
<td>Phase II randomized study of soy protein in postmenopausal women with breast disease taking tamoxifen and experiencing hot flashes</td>
<td>CALGB-79805</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>Pycnogenol® (Horphag Research Ltd., Guernsey, Channel Islands)</td>
<td>Pycnogenol® for the treatment of lymphedema of the arm in breast cancer survivors</td>
<td>R21 AT0011724-01</td>
</tr>
<tr>
<td>Chemotherapy-induced nausea and vomiting</td>
<td>Ginger</td>
<td>Phase II randomized study of ginger in patients with cancer and chemotherapy-induced nausea and vomiting</td>
<td>CCUM-0201</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Levocarnitine (L-carnitine)</td>
<td>Phase II randomized study of levocarnitine (L-carnitine) for the treatment of fatigue in patients with advanced cancer and serum carnitine deficiency</td>
<td>BIDMC-16101</td>
</tr>
</tbody>
</table>

Note. Search was conducted April 2004. Search strategy: all cancer trial types, phases, ages, and locations (limited to separate search category of CAM) in Physician Data Query® (PDQ). Hand search of all cancer trial types, phases, ages, and locations from paper printout of 2,273 cancer trials from ClinicalTrials.gov. Check PDQ and ClinicalTrials.gov for other protocol identifications.
References


