Clinical Trials in Cancer Part I
Biomedical, Complementary, and Alternative Medicine: Finding Active Trials and Results of Closed Trials

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Cancer clinical trials are research studies of humans designed to answer specific questions related to cancer. Meticulously conducted cancer clinical trials are the fastest method to establish safe and effective preventive, diagnostic, treatment, and supportive care interventions (National Cancer Institute [NCI], 2004). Complementary and alternative medicine (CAM) is a pervasive component in cancer care, and cancer CAM clinical trials are increasing in number and expanding in design. Oncology nurses are at the forefront of clinical supportive care for patients enrolled in clinical trials. They also are involved in designing clinical trials, accruing participants, monitoring, managing and analyzing data, and reporting results.

The author of this article performed a search for conventional biomedical and CAM clinical trials in the United States and offers a synopsis of how to locate active trials and published results. Part II of this article, to be published in a future issue, will review 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.

Types of Clinical Trials

Six predominant types of clinical trials exist: prevention, screening, diagnostic, treatment, supportive care, and genetic studies (NCI, 2004). Treatment trials studying new therapies or new indications of drugs, vaccines, and approaches to treatment compose the majority of clinical trials. Supportive care trials studying ways to improve cancer-related symptoms and quality of life are the second most common type of trial. Ancillary studies such as those that examine quality of life or pharmacoeconomics and nursing companion studies (Aitkin, 2000; Hohenstein, 2000; Tokarsky, 2000) can be categorized in one of the previously mentioned trial types. Although all trial types are conducted for conventional biomedical interventions, only three trial types currently are conducted for cancer CAM clinical trials: prevention, treatment, and supportive care. Table 1 offers explanations of all trial types with examples.

Phases of Clinical Trials

Three main phases of clinical trials exist: phase I, II, and III. Phase I trials generally involve a small number of patients (N < 50) and focus on how, when, and at which dose a new drug should be given. Phase II trials generally involve one type of cancer, focus on drug safety and efficacy, and comprise the majority of conventional biomedical and cancer CAM clinical trials. Phase III trials generally involve a larger number of patients (N > 100), use randomization, and compare new approaches with standard ones. Phase I and III trials are fewer in number for conventional biomedical and cancer CAM clinical trials. After a treatment has been approved by the U.S. Food and Drug Administration (FDA) and is marketed, it is studied in a larger, phase IV trial (N > 1,000) to evaluate side effects that were not apparent in the phase III trial. The author performed a single search in the NCI Physician Data Query® (PDQ) database for cancer clinical trials (N = 1,982 trials) and CAM clinical trials (N = 102 trials). See Figure 1 for a comparison of trials by phase.

Locating Clinical Trials

Despite increased interest in CAM clinical trials in general, only 3%–5% of patients with cancer in the United States participate in any type of clinical trials (Varricchio, McCabe, Trimble, & Korn, 1996). Typical sponsors of trials are NCI-generated programs such as the Cancer Centers Program, Clinical Trials Cooperative Group Program, Cancer Trials Support Unit, Community Clinical Oncology Program, and the National Institutes of Health (NIH) Clinical Center. Pharmaceutical and biotechnology companies sponsor trials that take place in academic centers, hospitals, clinics, and doctors’ offices. A metasearch for eligible databases revealed four optimal sources for retrieving clinical trial information related to cancer care in the United States: Center Watch™ Clinical Trials Listing Service, ClinicalTrials.gov, PDQ, and Trial Check™. These databases provide varying levels of access for healthcare providers, patients, and researchers (see Table 2).

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The author searched the databases for active, open trials on a single occasion in April 2004. Search strategies for each database began with “cancer clinical trials” including all types, phases, ages, and locations. Tailored search strategies using the following controlled vocabulary terms were performed to extract cancer CAM clinical trials using “or” as a Boolean search term: acupuncture, alternative, antineoplastons, black cohosh, botanicals, complementary, diet, energy healing, enzymes, flax seed, folic acid, fruits, garlic, ginger, healing, healing touch, herbal extracts, isoflavones, juices, juven, lycopene, massage, milk thistle, minerals, mistletoe, neovastat, quality of life, soy, supplements, vegetables, vitamins, and zinc. These terms were selected following an advanced search of “complementary and alternative medicine” trials in PDQ.

**Center Watch Clinical Trials Listing Service** holds about 41,000 active industry- and government-sponsored clinical trials in the United States and is designed for patients and research professionals. Trials listed by medical area (e.g., oncology, rheumatology) are in the “Patient and General Resources” section. Trials listed by drug profile (e.g., mechanism of action, indication for use) are in the “Industry Professional Resources” section. A single search returned 130 cancer trials and no CAM trials.

**ClinicalTrials.gov** holds about 10,000 clinical studies and is sponsored by NIH, other federal agencies, and private industry in 50 states and 90 countries. The National Library of Medicine (NLM) developed the site in collaboration with the FDA as a result of the FDA Modernization Act, which was passed into law in November 1997. Under the act, information about phase II and III trials conducted by the pharmaceutical and biotechnology industries under an investigational new drug application must be submitted to ClinicalTrials.gov. Recently, collaboration between NLM and NCI has resulted in a sharing and exportation of cancer trials from ClinicalTrials.gov into PDQ (including cancer CAM). A single search returned citations of 273 cancer trials that were then hand searched to identify 144 cancer CAM trials. An individual CAM selection is not an option when searching this database.

**PDQ** holds about 2,000 trials in its international registry and is maintained by NCI. Through PDQ summaries, it provides current, accurate cancer information for healthcare professionals and the public through peer-reviewed summaries on cancer treatment, screening, prevention, genetics, supportive care, and CAM. In addition, directories of physicians, professionals who provide genetics services, and organizations that provide cancer care are listed. NCI-sponsored trials are listed in PDQ as requested by the Cancer Treatment and Evaluation Program. A single search returned 2,043 cancer trials and 102 cancer CAM trials. Submission of CAM clinical trials for listing in PDQ has...
been and remains optional for principal investigators. 

**Trial Check** holds about 300 trials and is available to members of the Coalition of National Cancer Cooperative Groups, Inc., NCI-sponsored cooperative groups, American Society of Clinical Oncology (ASCO), and Oncology Nursing Society. Institutional and patient advocate members of the coalition also may use Trial Check. A single search returned 359 cancer trials that were hand-searched to find 9 CAM trials.

### Which Complementary and Alternative Medicine Modalities Are in Clinical Trials Now?

Six major categories encompass the wide range of modalities in the field of CAM: alternative medical systems, manipulative and body-based methods, energy therapies, mind-body interventions, nutritional therapeutics, and pharmacologic and biologic treatments. Alternative medical systems are built on completed systems of theory and practice, acupuncture, homeopathy, and traditional Chinese medicine, for example. Trials involving acupuncture to relieve pain, nausea, and vomiting are ongoing. Manipulative and body-based methods involve movement of body parts, such as reflexology and chiropractic medicine. A trial involving massage therapy for the relief of pain currently is accruing patients. Energy therapies involve the use of energy fields, such as Reiki and energy healing, both of which are in clinical trials. Techniques to enhance the mind’s capacity to affect bodily function and symptoms are termed mind-body interventions. Distance healing, guided imagery, and aromatherapy are examples. Music therapy and group therapy, among other mind-body interventions, are in clinical trials. The bulk of cancer CAM trials involve nutritional therapeutics. This category includes nutrients, non-nutrients, and bioactive food components used to prevent or treat cancer or its side effects and includes dietary regimens, supplements, antioxidants, vitamins, fruit and vegetable extracts, and minerals. Illustrations in clinical trials are soy protein isolates, valerian officinalis, hypericum perforatum, ginger, and garlic. Other examples are L-carnitine, black cohosh, zinc sulfate, vitamin E, selenium, lycopene, and folic acid. Pharmacologic and biologic treatments are drugs, vaccines, and other biologic interventions not yet accepted in conventional biomedical cancer care. Antineoplaston trials fall into this category. A subcategory of the larger category is complex natural products that consist of an assortment of plant samples (botanicals) and extracts of crude natural products. In clinical trials are shark cartilage, milk thistle, Pycnogenol® (Horphag Research Ltd., Guernsey, Channel Islands), Chinese herbal extract, and kanglaite injection. Table 3 illustrates the CAM modalities in active cancer clinical trials as retrieved in April 2004. The NCI CAM definitions and main classifications in the table offer a usable framework for enhanced understanding of the intricate, multifaceted field of CAM as a whole and cancer CAM as a subcomponent.

### Locating Published Results

Scientific articles reporting results from conventional biomedical and cancer CAM clinical trials are posted on Web sites, printed in biomedical journals, and searchable in online databases. PDQ offers two Web site avenues to find results: PDQ under the “closed trials” option in the advanced search mechanism and PDQ CAM Information Summaries. ASCO abstracts and presentation slides from the group’s national conferences are viewable on its Web site one to two weeks after the events. Search results illustrate the number of applicable abstracts, abstract year and number, cancer category, complete citation with all authors, complete abstract, and existing seminar slides. ASCO also publishes the *Journal of Clinical Oncology* and sponsors the People Living With Cancer Web site.

The NLM provides access to published results of clinical trials through a choice of options. First, printed national and international biomedical journals are indexed at the NLM (located on the NIH Campus in Bethesda, MD), including peer-reviewed and nonpeer-reviewed journals, some of which are available in full text online. Individual and institutional subscriptions are available. Copies of printed publications are available through the Loansome Doc Ordering System following registration (requires institutional or educational affiliation). PubMed and MEDLINE®, sponsored by NLM, provide a CAM limit in searching for abstracts only in CAM journals (viewable under the “Limits” option when searching a topic). The final area is MEDLINE Plus®, which is a service of NLM and NIH that presents updated health information after clinical trials.

Two larger, international searchable databases for accessing results of clinical trials are the Cochrane Library and the Excerpta
TABLE 3. COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) MODALITIES IN CLINICAL TRIALS

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION</th>
<th>EXAMPLES</th>
<th>MODALITIES IN CLINICAL TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative medical systems or their</td>
<td>Systems built on completed systems of theory and practice</td>
<td>Traditional Chinese medicine, acupuncture, ayurveda, homeopathy, naturalpathy, and Tibetan medicine</td>
<td>Acupuncture, acupressure, electroacupuncture, and Traumeel S® (homeopathy) (Heel Company, Baden-Baden, Germany)</td>
</tr>
<tr>
<td>components</td>
<td></td>
<td></td>
<td>Massage therapy</td>
</tr>
<tr>
<td>Manipulative and body-based methods</td>
<td>Methods based on manipulation or movement of parts of the body</td>
<td>Chiropractic, therapeutic massage, osteopathy, and reflexology</td>
<td>Energy healing, energy therapy, and Reiki</td>
</tr>
<tr>
<td>Energy therapies</td>
<td>Therapies involving the use of energy fields</td>
<td>Reiki, therapeutic touch, pulsed fields, and magnet therapy</td>
<td>Distance healing, exercise-based counseling, group therapy, healing touch, music therapy, spirituality and religiosity, standard counseling, stress management training</td>
</tr>
<tr>
<td>Mind-body interventions</td>
<td>Techniques designed to enhance the mind’s capacity to affect bodily function and symptoms</td>
<td>Meditation, hypnosis, art therapy, biofeedback, mental healing, imagery, relaxation therapy, support groups, music therapy, cognitive-behavioral therapy, prayer, dance therapy, psychoneuroimmunology, aromatherapy, and animal-assisted therapy</td>
<td>None</td>
</tr>
<tr>
<td>Movement therapy</td>
<td>Modalities used to improve patterns of bodily movement</td>
<td>Tai chi, Feldenkrais, Hathayoga, Alexander technique, dance therapy, QiGong, Rolffing, Trager method, and applied kinesiology</td>
<td>Black cohosh, creatine, curcumin, flax seed, folic acid, fruit and vegetable extracts, garlic, ginger, herbal therapy, juen, L-carnitine, low-fat diet, lycopene, macrobiotic diet, Noni fruit extract, nutritional supplements, pomegranate juice, selenium, soy protein isolate, vitamins C and E, and zinc sulfate Antineoploasts, pancreatic proteolytic enzymes, and hyperbaric oxygen</td>
</tr>
<tr>
<td>Nutritional therapeutics</td>
<td>Assortment of nutrients, non-nutrients, and bioactive food components that are used as chemopreventive agents and the use of specific foods or diets as cancer prevention or treatment strategies</td>
<td>Dietary regimens such as macronutrients, vegetarian, Gerson therapy, Kelley/Gonzalez regimen, vitamins, dietary macronutrients, supplements, antioxidants, selenium, coenzyme Q10, and orthomolecular medicine</td>
<td>None</td>
</tr>
<tr>
<td>Pharmacologic and biologic treatments</td>
<td>Drugs, complex natural products, vaccines, and other biologic interventions not yet accepted in mainstream medicine, off-label use of prescription drugs. Interventions that have conventional therapeutic applications generally are not used for cancer treatment promoted by cancer CAM practitioners.</td>
<td>Antineoploasts, products from honey bees, 714-X, low-dose naltrexone, met-enkephalin, immunoaugmentative therapy, laetrile, hydrazine sulfate, NewCastle virus, melatonin, ozone therapy, thymus therapy, enzyme therapy, and high-dose vitamin C</td>
<td>None</td>
</tr>
<tr>
<td>Complex natural products</td>
<td>Subcategory of pharmacologic and biologic treatments, consisting of an assortment of plant samples (botanicals), extracts of crude natural substances, and unfractonated extracts from marine organisms used for healing and treatment of disease</td>
<td>Herbs and herbal extracts, mixtures of tea polyphenols, shark cartilage, Essiac tea, cordyceps, sun soup, MGN-3, and mistletoe</td>
<td>Chinese herbal extract, green tea extract (polyphenol E), kalglaite injection, milk thistle, mistletoe, Pycnogenol®, shark cartilage, St. John’s wort, valerian, and Virulizin® (Lorus Therapeutics, Ontario, Canada)</td>
</tr>
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</table>

Medica Database (EMBASE). The Cochrane Library is a collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews. The abstracts of Cochrane Reviews can be browsed or searched and are available without charge to the public. Sixty-four abstracts involving CAM are available. The Cancer Library is a new electronic resource that includes a collection of more than 100 cancer reviews, summaries and commentaries of Cochrane Reviews, systematic reviews of the effects of cancer treatments, and a register of published controlled cancer trials. EMBASE is a comprehensive biomedicine and pharmacology database with reportedly more than 9.5 million records currently in the database and an international journal collection of 4,500 biomedical journals from 70 countries. EMBASE on ScienceDirect® is updated weekly and available to institutions via license agreement. Once a user is registered, the database is accessible via password. Several CAM journals not indexed in PubMed are indexed in ScienceDirect. To learn how to access results of a closed trial using PDQ, see inset.

Challenges in Identifying Complementary and Alternative Medicine Modalities in Clinical Trials

The immediate challenges to identifying cancer CAM clinical trials not only in the four major databases searched but also in the...
healthcare community are the lack of a standard definition of CAM, variations in coding of clinical trials, and the optional listing of conventional and CAM trials in any database in the United States. The lack of a standard definition of CAM is well recognized. The multiple definitions that exist in addition to a blurred understanding of what constitutes standard therapy are additional components. The various interventions to enhance quality of life are used in mainstream cancer care and are not solely CAM. However, through the use of CAM interventions such as guided imagery and therapeutic touch, quality-of-life enhancement techniques can be considered CAM. Furthermore, natural products in clinical trials may have an investigational new drug designation and be used for cancer treatment but are derived from what is considered a CAM source (such as shark cartilage). When cancer clinical trials are added into databases such as PDQ, a coding process takes place to designate the type of trial and treatment or intervention. A prior focus on conventional biomedical cancer modalities and decreased exposure to CAM modalities in clinical trials lead to undercoding of cancer CAM clinical trials. Although not complete, PDQ remains the only database that has a “Complementary and Alternative” treatment subgroup as a selection option and, therefore, is the premier location for accessing trials of CAM clinical trials. Introduction.

Summary

Most cancer CAM clinical trials are treatment or supportive care trials in phase I, II, or III status. A recent search showed that, at present, a very limited number of retrievable pharmaceutical- or industry-sponsored cancer CAM clinical trials is listed in publicly accessible databases. Two databases, Center Watch and Trial Check, focus on industry, healthcare providers, and patient advocate groups and have fees or limited access. As more clinical trials are imported from NLM’s Clinical Trials.gov to NCI’s PDQ database, more cancer CAM trials will be accessible and free to the public. Published results from clinical trials are available in multiple locations and retrievable with advanced searching but remain of limited access to most of the public because of academic or hospital library subscription services. All cancer clinical trial results are not likely to be housed in one location (either via database or in print); thus, cancer CAM clinical trial results likely will not be either. Because PDQ currently is the central location for cancer CAM clinical trial listings in the United States, the database should be expanded to include published results that are retrievable by healthcare professionals and the lay public free of charge. In clinical and research roles, oncology nurses are compelled to keep abreast of advances in cancer care, especially in the realm of cancer clinical trials. Keeping abreast of results of cancer CAM clinical trials is vital for oncology nurses in patient education, advocacy, and advancement of evidence-based practice.

References


