

# Bringing Evidence to Complementary and Alternative Medicine for Children With Cancer

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Over the past decade, we pediatric oncologists, along with most practitioners trained in the Western medical tradition, have struggled with the fact that our patients are using complementary and alternative medicine (CAM) at increasing rates. Studies have shown that 31% to 84% of children with cancer<sup>1–14</sup> and approximately 30% of adults with cancer<sup>15</sup> will utilize some form of CAM during their treatment regimen. The use of CAM as a social phenomenon has been well documented<sup>16</sup> and was initially consumer driven, often with physicians as an oppositional force. Increasingly, however, conventionally trained medical scientists have been designing and conducting research studies evaluating the safety and efficacy of CAM modalities. Pediatric research studies are particularly important as results from studies in adults cannot always be extrapolated to a pediatric population because of children's unique developmental, social, and metabolic aspects. This report, and the others in the series to follow, will attempt to define the scope of CAM use in the pediatric oncology population and the issues which ensue from its use, and outline several intriguing research avenues.

The term CAM has become a convenient acronym to describe a broad domain of healing resources that refers to those therapies generally falling outside the mainstream of conventional medicine. "Complementary" has referred to those methods that augment conventional therapies, and "alternative" has referred to methods used instead of mainstream treatments. CAM therapies for cancer encompass a wide variety of approaches, including touch therapies such as massage, mind-body medicine

techniques such as hypnosis, energy healing, acupuncture, and nutritional and pharmacologic therapies such as herbs and other dietary supplements. The National Center for Complementary and Alternative Medicine defines CAM therapies in 5 main domains (Table 1, Ref 17). The boundaries between CAM and conventional medicine are not always clearly defined, because the list of practices considered CAM changes continually as those therapies that are proven safe and effective through research, and become accepted as mainstream. The newer term "integrative oncology" implies an evolving evidence-based specialty that uses complementary therapies in concert with medical treatment to enhance efficacy, improve symptom control, alleviate patient distress and reduce suffering.<sup>18</sup> For the purposes of these reports, we will employ the less comprehensive but more commonly used term CAM.

The treatment of children with cancer is one of the great medical success stories of the latter half of the 20th century. The diagnosis of acute lymphoblastic leukemia has gone from a certain death sentence to a disease with an almost 80% cure rate in some subgroups. More than three-quarters of all children diagnosed with cancer will now be cured.<sup>19</sup> This is in contradistinction to many adults in whom cancers are now being treated almost as chronic conditions, rather than as curable diseases. These remarkable gains have all been through careful, cumulative research, primarily under the umbrella of cooperative trial groups, sponsored by cooperative groups throughout the world. The rationale has been that the number of children with cancer is relatively low, and that few single institutions will have sufficient numbers to answer important questions. A similar approach is important as we seek to answer questions about CAM use in children. For example, a Complementary Therapies Task Force was initiated at the April 1998 Children's Cancer Group (CCG) meeting under the auspices of the Epidemiology and Cancer Control Strategy Group. The task force was charged with evaluating the potential role of CCG in conducting research and providing information in the rapidly growing field of complementary medicine. With the merger of CCG and the Pediatric Oncology Group into the Children's Oncology Group (COG), the task force has evolved into the Complementary and Alternative Medicine (CAM) Subcommittee of the Cancer Control Committee. The long-term goals of the Committee are to promote scientific investigation of complementary therapies as they relate to childhood cancer and to

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**TABLE 1.** Categorization of CAM Therapies by the National Center for Complementary and Alternative Medicine<sup>17</sup>

Type of CAM	Definition	Examples
Alternative medical systems	Complete systems of theory and practice	Homeopathy, naturopathy, Traditional Chinese Medicine, Ayurvedic medicine
Mind-body medicine	Variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms	Meditation, prayer, mental healing, art, music, dance
Biologically based therapies	Substances found in nature	Dietary supplements, herbal products, and the use of other so-called natural but as yet scientifically unproven therapies
Manipulative and body-based methods	Manipulation and/or movement of one or more parts of the body	Chiropractic or osteopathic manipulation, massage
Energy Therapies Biofield therapies	Are intended to affect energy fields that purportedly surround and penetrate the human body	Qi gong, Reiki, therapeutic touch
Bioelectromagnetic-based therapies	Involve the unconventional use of electromagnetic fields	Pulsed fields, magnetic fields, or alternating current or direct current fields

provide reputable information on these therapies to health care providers and patients. The CAM Subcommittee's primary goal, however, is to design and execute intervention-based clinical trials to evaluate the efficacy of specific complementary therapies in use by children with cancer.

Most of the initial research on CAM in pediatric cancer relied upon surveys to determine prevalence of CAM use. In 1977, Faw et al<sup>1</sup> found that 7.7% of the patients surveyed were using CAM; more recent studies have found much higher figures, between 31% and 84%.<sup>20</sup> Most parents surveyed chose to use CAM for their children to combat side effects of the cancer or the cancer therapy; CAM is rarely used as the primary means to treat the cancer. The most common therapies used were prayer and spiritual healing, nutritional supplements, vitamins, massage, and mind-body therapies.<sup>6,7,9,21</sup> The inclusion of prayer in CAM surveys is controversial and is felt by some researchers to unfairly inflate estimates of CAM use. Factors associated with CAM use are poor prognosis, prior CAM use by the parent, higher parental education, older age, and religiosity.<sup>7,8,13</sup> Of great concern to pediatric oncologists is the fact that only half of the respondents disclose their use of CAM to their providers,<sup>4,6,9,13</sup> and that many children enrolled on cooperative group trials were also using CAM, adding yet another potentially confounding factor to already complicated trial designs.<sup>9</sup>

Surveys such as the ones referred to above help to identify areas for further research. The current emphasis of the CAM subcommittee in COG is to move away from descriptive studies and toward interventional studies. The majority of studies to date investigating CAM in children with cancer have focused on CAM as supportive care agents and have been limited institution projects, with plans to move promising agents or modalities to group-wide trials.

This is not without its difficulties. We have discovered several barriers to mounting large-scale research studies of complementary therapies through COG. There are many different types of CAM therapies

in use by children with cancer and very few have been evaluated for safety and efficacy. There is often little preexisting literature even in adults with cancer to guide the prioritization of research studies. In addition, firmly held preconceptions by physicians, patients, and complementary/alternative medical practitioners about individual therapies have made the design and execution of studies difficult. Institutional review boards at individual institutions have been reluctant to "take on" potentially controversial complementary modalities. As CAM has become more accepted throughout the medical community, these issues have become less problematic. Many academic institutions, for instance, now have departments of integrative medicine.<sup>22</sup> Nonetheless, the obstacles to designing and implementing CAM studies on a large scale are instructive.

At the end of 2005 there were 2 open COG group-wide CAM trials. **ACCL0331**, A Randomized Double Blind Placebo Controlled Clinical Trial to Assess the Efficacy of Traumeel S (IND No. 66649) for the Prevention and Treatment of Mucositis in Children Undergoing Hematopoietic Stem Cell Transplantation, opened in April 2004 and is nearing completion. This study was based upon an Israeli pilot study that showed that the homeopathic medication Traumeel S significantly reduced the severity and duration of chemotherapy-induced mucositis in children undergoing bone marrow transplantation.<sup>23</sup> The "gold standard" of the randomized, double blind, placebo controlled study design was a positive factor in the study's acceptance group-wide, but the complex nature of the homeopathic remedy, which contains highly diluted extracts from 14 plants and minerals, was not familiar to most COG members or their institutional review boards.

**ACCL04C2**, A Randomized Study of Electroacupuncture Treatment for Delayed Chemotherapy-Induced Nausea and Vomiting in Patients with Pediatric Solid Tumors opened in December 2005. This study had originally opened at the National Cancer Institute in 2002, but accrual was slow so COG was asked to participate. There are few studies to date involving

children and acupuncture, in part because of a concern that children would not accept placement of needles, although there is a general consensus that acupuncture is acceptable to children beginning at age 10 years. Acupuncture studies are also difficult because they generally involve the use of “sham” points, because the mere act of manipulation of needles or simply provider attention may have therapeutic impact. However, as prolonged delayed nausea is still a clinical challenge, this study has real potential to identify a useful adjunctive agent.

Several other studies are in various stages of design throughout the COG structure. The CAM subcommittee is collaborating with other Cancer Control Subcommittees such as Nursing and Nutrition to design high-impact studies addressing pressing issues such as fatigue and obesity. The goal is also to work with disease committees to ask questions that can be included in therapeutic trials as an upfront question, such as the use of milk thistle as a hepatoprotectant in children undergoing treatment for acute lymphoblastic leukemia. Finally, the possibility of developing botanical agents with direct anticancer properties such as curcumin is a particularly intriguing area for further research.

Many important questions remain to be studied. In particular, the high rate of self-administered use of biologically active adjuvant therapies such as antioxidants demands that we design studies that will examine the potential interaction between these agents and commonly used chemotherapy drugs. Certain chemotherapy agents, such as anthracyclines, and radiation both work in part by oxidative damage and the use of high doses of antioxidants may work to counteract these effects. On the other hand, antioxidants may have a valuable role in treating certain acute toxicities of conventional therapy. Immunomodulators are another broad category of CAM therapies that purportedly affect the immune system and include Asian mushrooms and mistletoe. These agents generally increase either cytotoxic T lymphocytes or natural killer cells, or increase endogenous production of cytokines. Whether these actions have *in vivo* efficacy to fight cancer is not well defined at the current time, but must be further studied. No definitive answer has been found to these vexing questions, and therefore children on therapy should be discouraged from combining chemotherapy and radiation with high doses of antioxidants, and those with leukemia or lymphoma or those who have had stem cell transplant should be discouraged from taking immunomodulators.

Adverse events have been reported with CAM therapies, especially from contamination of herbal products. Despite these caveats, however, no actual herb-drug interactions resulting in adverse outcomes have been reported in humans undergoing cancer treatment. Nonetheless, caution should be employed in recommending biologically active agents. Tremendous strides have been made in the care of children with cancer, and we should not allow potentially life-saving therapies to be shortchanged in an effort to provide a less toxic, or more “natural” therapy.

Existing research demonstrates beneficial roles for some CAM therapies. Mind-body medicine and biofield therapies may be particularly useful, especially for the management of symptoms for which conventional therapy is often ineffective. Hypnosis and imagery reduced anticipatory nausea and vomiting and pain in children with cancer.<sup>24-27</sup> Music therapy may affect a child’s emotional state<sup>28</sup> and immune function.<sup>29</sup> Body-based therapies such as massage are associated with improvements in mood and anxiety.<sup>30</sup>

Over the year, the Journal of Pediatric Hematology/Oncology will publish several more reports related to the use of CAM in children with cancer. In particular, CAM use in children raises unique legal and ethical issues. Michael Cohen will address the legal issues applicable to pediatric oncologists integrating CAM therapies into clinical care, including licensure of CAM practitioners and malpractice risk. The efficacy of some CAM therapies (and some conventional therapies) cannot be easily evaluated in the context of randomized double blind placebo controlled clinical trials. Lillian Sung and Brian Feldman will discuss some novel therapeutic designs that can be used to overcome some of the methodologic difficulties encountered in designing trials of CAM.

The major concern among pediatric oncologists is the potential for interactions among biologically based therapies and conventional treatments, especially chemotherapy and radiation therapy. The observation that the concomitant use of irinotecan with St John’s Wort results in low levels of irinotecan through induction of cytochrome P450 CYP3A4 warrants further attention to this issue.<sup>31</sup> Although there are many theoretical concerns about the potential pharmacokinetic interactions of dietary supplements and chemotherapy, limited data exists, especially in children. Sylvain Baruchel will address the risks of dietary supplement interactions. Some CAM therapies have potential anticancer activity. Steven Melnick will outline new developmental therapeutic avenues with a focus on those agents that may be active in childhood cancer, with specific examples from the Ayurvedic tradition.

Many CAM therapies have the potential of improving quality of life. CAM therapies may be considered in the management of symptoms of cancer and conventional treatment and for psychologic support associated with the diagnosis of cancer. CAM therapies may also be useful for end of life care. Several programs integrate CAM therapies into the conventional care of a child with cancer. Janice Post-White and Elena Ladas will explore in depth the use of CAM as supportive care modalities. They will also provide educational resources about CAM to guide the clinician as well as parents and patients.

International Society of Pediatric Oncology (SIOP) recently published guidelines that called for the health care team to be attentive to complementary therapies that may be physically or psychologically harmful to children and their parents but also indicated that the health care team should not automatically and

dismissively discourage the use of nonharmful complementary therapies.<sup>32</sup>

Many health care providers working with children with cancer have expressed the need for reputable information resources to help guide discussions on CAM with the patients and families. The goal of this series is to serve as a starting point for information on the issues surrounding CAM that will be useful for all those that care for children with cancer.

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