



Integrative therapies for children with hematological malignancies

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Evidence for integrative therapies (IT) in children with hematological malignancies is slowly evolving. The ideal model of integrative pediatric oncology would offer IT modalities that are deemed safe and effective in conjunction with effective conventional medical treatments. Because of potential interactions, herbs and other dietary supplements should be used with caution, especially during active therapy. Health and wellness should be the emphasis, with IT therapies supporting health promotion and key disease prevention strategies for childhood cancer survivors. All uses, responses, and effects of IT therapies should be carefully documented. A desire to use IT therapies may be an effort to become an active participant in the healing process. Health care providers should encourage, not discourage, this partnership.

Many parents of children with cancer explore the use of integrative therapies (IT) to help manage the side effects associated with cancer therapy, to augment the efficacy of conventional medications, and to provide psychological support for coping with the diagnosis of cancer. Children with cancer are significant consumers of modalities classified as IT, with international surveys demonstrating 31% to 84% reportedly using such therapies.¹ Specific prevalence data on the use of IT among children with hematological malignancies has generally not been reported in the surveys, although IT were used by 53 of 60 children with leukemia in a recent Malaysian study.² Most children use these therapies in an “integrated” approach with conventional therapies; relatively few reports describe the use of alternative therapies in lieu of conventional medicine, although 5 of 6 cases involved children with good prognosis hematological malignancies.³ Parents pursue IT in order to ensure that they have left “no stone unturned” and to feel as if they are doing all they can to help their child be cured or support them during cancer therapy. The high prevalence of IT use, especially the dietary supplements used in combination with conventional agents, has brought attention to the potential for adverse interactions. Although there has been a significant increase in research on IT for cancer, there is still a paucity of data to guide clinical practice incorporating IT for children with hematological malignancies.

Why Are IT Controversial in the Care of Children with Hematological Malignancies?

Similar to the situation in adults, the integration of complementary therapies in the management of children with

leukemia and lymphoma is controversial. Most surveys demonstrate that the biologically active herbs and other dietary supplements are the most common type of IT in use with conventional therapies,^{1,4} yet there are very few clinical trials in adults or children examining their safety and efficacy. Adverse events have been reported,⁵ especially related to contamination of botanical products from China or India with heavy metals such as lead, mercury, and arsenic, which have, among other things, the potential to interfere with cognitive development in the young child. Microbial contamination of herbal products may be associated with even more significant risks in immunocompromised children, especially for those children undergoing stem cell transplantation. Direct toxicities of dietary supplements have been observed, but the prevalence is unknown as systematic reporting is not legally mandated.

The non-biologically based therapies are generally considered safe. For example, in a review of adverse events observed among children receiving acupuncture, the incidence rate of side effects is estimated to be only 1.55 per 100 treatments, with the most common side effect being redness at the puncture site.⁶ Only 1 serious adverse event was observed among 1865 treatments. Although there is a low risk of interference with conventional therapies, training programs for IT practitioners often have little to no standards for training with children, let alone children receiving intensive conventional treatment for hematological malignancies.

To date, most pediatric hematology/oncology fellowship curricula have not incorporated formal educational oppor-

tunities on integrative therapies.⁷ The importance of addressing the use of IT among children with cancer has been underscored by guidelines issued by the International Society of Pediatric Oncology (SIOP), which recommend that the health care team (1) should be attentive to complementary therapies that may be physically or psychologically harmful to children and their parents, and (2) should not automatically and dismissively discourage the use of non-harmful complementary therapies.⁸

Research Barriers

With the greater use of IT by children with hematological malignancies, increasing scientific attention is being directed towards the investigation of these therapies. Research has evolved from testimonials of “miraculous” cures, case series and single arm outcome studies to underpowered clinical trials and, more recently, to randomized clinical trials investigating efficacy.⁹ However, research on IT is complex and usually more difficult than that of conventional anticancer therapies. Preclinical and phase I studies are often not done, and this may impact the conduct of phase III trials. Additional barriers to research efforts in children with cancer exist. For example, investigations of non-pharmacologic therapies such as acupuncture are further hampered by the lack of validated assessment tools

in children. The rarity of childhood cancer further reduces the incentive for many IT providers to scientifically evaluate therapies in children. Despite these limitations, evidence is available from research studies including randomized controlled trials to support the use of some IT for symptom control among children with hematological malignancies (Table 1).^{10,11}

Direct Anti-leukemia or Lymphoma Effects

Most parents are also interested in the potential anti-cancer properties of herbs and other supplements; however, in this area clinical trial data are nonexistent. Preclinical studies have investigated a limited number of botanicals in the setting of childhood leukemia and lymphoma. For example, in preclinical studies of curcumin treatment of patient acute lymphoblastic leukemia (ALL) cells, modulation of leukemia cell resistance was achieved through a reduction in multiple drug resistance gene mRNA levels.¹² In another study, *Annona glabra* (pond apple) extracts were highly cytotoxic to drug-sensitive (CEM) and multidrug-resistant leukemia (CEM/VLB) cell lines.¹³ In contrast, *in vitro* investigation of extracts of mistletoe (*Viscum album*) and two Peruvian herbs, *Uncaria tomentosa* (Vilcacora) and *Croton lechleri* (Sangre de drago) in 51 samples from patients with leukemia and 4 leukemia cell lines (Jurkat,

Table 1. Integrative therapies that have been investigated for use as a supportive care therapy in children with hematological malignancies (reviewed in Ladas et al¹⁰ and Myers et al¹¹).

Symptom	Alternative medical systems	Mind-body medicine	Biologically based therapies	Manipulative and body-based methods	Energy therapies
Nausea/vomiting	Acupressure (-)	Cognitive Distraction* (+) Hypnosis* (+) Music* (+)	Massage (-)	ns	ns
Mucositis	Homeopathic mouth rinse* (+/-)	ns	Glutamine* (+)	ns	ns
Pain	ns	ns	ns	Massage* (-)	ns
Procedural pain	ns	Music (+) Hypnosis* (+) Art (+)	ns	ns	ns
Fatigue	ns	ns	ns	Massage* (-)	ns
Cachexia	ns	ns	Fish oil* (+)	ns	ns
Anxiety/Insomnia	ns	Hypnosis* (+)	ns	Massage* (+)	ns
Weight gain	ns	ns	Creatine (+)	ns	ns
Constipation	ns	ns	ns	ns	ns
Hepatotoxicity	ns	ns	Milk thistle* (+)	ns	ns
Mood	ns	ns	ns	Massage* (+)	ns

*Randomized controlled trial
(+) Positive results observed
(-) Negative results observed
ns indicates not studied.

CCRF-CEM, HL-60, K-562) demonstrated stimulation of cell growth.¹⁴ However, generalization of these findings from limited sets of experiments with selected products of unknown composition limits the significance of the results. At the current time, no active clinical research trials investigating botanicals or other dietary supplements in children with hematological malignancies are in progress.¹⁵

In addition to evaluation of direct anti-cancer activity, the investigation of the interactions of specific dietary supplements with conventional chemotherapy and radiation therapy is an area of pressing need. Antioxidants are one of the most common classes of supplements used by patients with cancer; these supplements are used for direct cytotoxic effects, for synergy with conventional therapy or to mitigate conventional therapy-induced toxicity. In a prospective observational study conducted among children with ALL, low plasma¹⁶ and dietary antioxidant¹⁷ levels directly correlated with treatment-related toxicity. Studies evaluating the impact of supplementation on toxicity and leukemia-free survival have not been completed. The effect of immune-enhancing dietary supplements in children with hematological malignancies is also a priority area for research. Popular immune-enhancing herbs and dietary supplements include astragalus, echinacea, beta-glucans, and mushroom extracts (especially reishi, maitake, and shitaki). No clinical trials specifically in children have been reported in the English language literature.

Practicing Integrative Oncology in the Care of Children with Hematological Malignancies

There are many aspects of childhood cancer therapy where IT may have a beneficial role, especially as a component of the multidisciplinary approach often utilized in childhood cancer therapy. The aims of the IT interventions are to assist with the minimization of pain and suffering and to provide practical, emotional and physical support. These therapies may be a particularly good resource for children whose illness or conventional treatment involve an extended period in the hospital, such as children with newly diagnosed ALL or acute myeloid leukemia, children undergoing stem cell transplants, and children in the end-of-life setting. Children may become fatigued and often have reduced muscle tone. IT interventions such as yoga, karate, and massage can help maintain movement, muscle tone, and strength. Massage or reflexology may ease muscle pain associated with corticosteroid or vincristine therapy. Long conventional treatment durations such as those for ALL include therapy for up to 3 consecutive years can also lead parents to search for more comprehensive approaches to the management of side effects or to investigate IT that may minimize long-term effects of cancer therapy. On the other hand, IT that require numerous patient visits or require

radical lifestyle modification may be unreasonable given the demands of conventional treatment regimens.

The decision to use a particular IT will in part be based on the developmental stage of the child. Children with fear of needles and discomfort with the invasiveness of the conventional treatment such as intrathecal chemotherapy injections and bone marrow aspirations may have added anxiety with the use of acupuncture; in this instance, acupressure or massage may be more appropriate options. Young children often have a fear of strangers and may assume that all health care providers may induce unintentional pain. Introduction of the relatively non-invasive IT modalities of reflexology, energy therapies, or aromatherapy may be a more effective strategy. This is particularly true for younger patients who may not have the language skills to articulate their fears, yet have strong imaginations to understand concepts such as energy fields, guided imagery, and meditation. Children and adolescents may be hesitant in using IT because of the fear of what the therapy may feel like; therefore, an effective strategy may be to first observe a session on another patient, parent, or sibling.

The health care provider must consider several important factors in children with cancer prior to supporting or discouraging the use of IT. Childhood cancers are generally quite different than those cancers observed in adults. For the most part, childhood leukemias and lymphomas are more sensitive to chemotherapy than those observed in adults, such that today nearly 80% of children can expect to be cured.¹⁸ For some cancers such as Hodgkin and non-Hodgkin lymphoma and some favorable subsets of ALL the cure rate is in excess of 90%. Children also tend to tolerate chemotherapy better, as they are less likely to have comorbid conditions. Therefore, it is critical that therapies that may interfere with or encourage refusal or delay of conventional therapies be avoided in the child with cancer. An often under-recognized observation is that IT are used frequently among children enrolled on clinical trials.⁴ Therefore, concomitant use of any IT must be recorded so that any potential interactions can be carefully monitored. The decision to include IT should be based on the available evidence and not include those therapies that require a tremendous burden with unproven benefit or that might lead to obstacles for the child to adhere to the conventional therapy.

Several types of integrative therapies can be considered for symptom control in the care of the child with hematological malignancies at this time (**Table 1**). Massage therapy, one of the most commonly reported IT among children with cancer, is used most often to cope with side effects associated with anticancer therapy, including pain, nausea, and fatigue. Preliminary data in adults suggest that massage

may also impact cortisol levels and/or NK cell number or activity.¹⁹ Mind-body therapies, especially hypnosis, cognitive distraction and music therapy, may be effective adjunctive therapies in managing procedural pain, anxiety and nausea.²⁰ Acupressure is well accepted but has not yet demonstrated efficacy for chemotherapy-associated nausea among children with ALL.²¹

Several dietary supplements have demonstrated efficacy for symptom control, especially for side effects for which there are limited conventional treatment options. Glutamine is safe and beneficial in reducing the severity of mucositis in children undergoing stem cell transplantation.²² Creatine monohydrate may attenuate corticosteroid-associated increases in body fat accumulation, a common complication of therapy for childhood ALL and lymphoma.²³ The hepatoprotective herb milk thistle is associated with reductions in serum transaminases in children receiving maintenance chemotherapy for ALL.²⁴

Integrative Therapies and Survivorship

Adult survivors of childhood leukemia and lymphoma are at risk for medical and psychosocial sequelae that may adversely affect their health status.²⁵ Survivors are challenged with issues not limited to energy balance, fatigue, bone health, pain syndromes, and anxiety and are at increased risk for many long-term sequelae, including cardiac dysfunction, stroke, osteoporosis and osteonecrosis, infertility, and second malignancies.²⁶ The use of IT extends into survivorship to reduce risk of relapse, cope with late effects from cancer therapy, or reduce their risk of developing a late effect.²⁷

The use of IT as a component of a healthy lifestyle may provide support to survivors for coping with many of the late effects of cancer therapy. For example, yoga and meditation may help to reduce the feelings of anxiety associated with cancer recurrence, may lessen the functional impact of disturbances in balance or gait, or assist with maintenance of a healthy weight. Acupuncture may provide relief to patients who are challenged with fatigue, recurrent pain or infertility.²⁸ Use of dietary supplements is less complicated as concerns for interactions with conventional chemotherapy or radiation therapy are not issues.

Integrative Therapies and Palliative Care

Pain and suffering at the end of a child's life is often not adequately managed with conventional approaches. The most common symptoms experienced by children at this time include fatigue, pain, dyspnea, anorexia, nausea and vomiting, constipation and diarrhea, with many of these symptoms not adequately treated by conventional means, as 89% of parents in one study reported that children suffered

“a lot or a great deal” within the last month of life.²⁹

Therapies to be considered for their adjunctive role include acupuncture, aromatherapy, massage, energy therapies, and mind-body approaches. Palliative care should include interventions offered to parents and siblings, who often suffer both psychological and physical distress during the child's end of life and consequent phase of bereavement.³⁰ A recent survey investigating the current practices and resources surrounding palliative and end-of-life care among participating institutions of the Children's Oncology Group demonstrated that integrative services were widely available: 39% of institutions directly provided services and 95% had services available in the communities that these institutions serve.³¹ Of the 50 institutions that offered IT, 76% of the oncology divisions made direct referrals for these therapies, highlighting the acceptance of IT in the palliative care setting.

How Can We Best Counsel Our Patients about Integrative Therapies?

As more parents of children with cancer seek integrative care, pediatric institutions face the need to answer questions from patients and healthcare providers about integrating these therapies in the care of children with hematological malignancies. In a study performed at a pediatric institution with an established IT consultation service, consultations were most frequently requested by oncology patients for assistance with symptom management and with questions on various therapies, especially herbs and dietary supplements.³² As healthcare providers, we educate patients and parents about their disease and the various treatment modalities available. Similarly, we need to offer easy-to-understand information about integrative approaches.

Table 2 lists reputable internet resources for clinicians and patients. We can encourage patients and parents to talk with us when they hear of anecdotal use of unproven modalities, and discourage the use of most biologically based IT until studies are undertaken to prove their safety and efficacy. Most of all, we can remind them that we are their partners in care, that we care about and take seriously their wishes to use IT in the best interests of their child.

Summary

The goal of an integrative approach in the care of children with hematological malignancies is to provide IT modalities that are deemed safe and effective in conjunction with effective conventional medical treatments. There is significant need for research evaluating the roles of IT for direct treatment of hematological malignancies and for symptom control of toxicities related to conventional therapies. Healthcare providers should consider how IT services may be beneficial for children with leukemia or lymphoma. However, until the evidence for or against an integrative

Table 2. Integrative oncology resources.**Government Resources**

National Center for Complementary Alternative Medicine, National Institute of Health:
<http://nccam.nih.gov>

Office of Cancer Complementary Alternative Medicine, National Cancer Institute, National Institute of Health:
<http://occam.nci.nih.gov>

PDQ® Cancer Information Summaries: Complementary and Alternative Medicine, National Cancer Institute, National Institute of Health:
<http://www.cancer.gov/cancertopics/pdq/cam>

Office of Dietary Supplements, National Institute of Health:
<http://ods.od.nih.gov/>

U.S. Food and Drug Administration, Department of Health and Human Services:
<http://www.fda.gov/>

Academic Institutions

Integrative Therapies Program for Children with Cancer, Columbia University Medical Center:
<http://integrativetherapies.columbia.edu/>

About Herbs, Botanicals and Other Products, Memorial Sloan Kettering Cancer Center:
<http://www.mskcc.org/mskcc/html/11570.cfm>

Complementary/Integrative Medicine, MD Anderson Cancer Center:
<http://www.mdanderson.org/departments/cimer/>

Zakim Center for Integrative Therapies, Dana Farber Cancer Institute:
<http://www.dana-farber.org/pat/support/zakim/default.html>

Databases

Natural Standard
<http://www.naturalstandard.com/>

Cochrane Reviews on Complementary Medicine, The Cochrane Collaboration:
http://cochrane.org/reviews/en/topics/22_reviews.html

CAM Clinical Trials from NCI's PDQ® Database:
http://www.cancer.gov/cam/clinicaltrials_pdq.html

CAM on PubMed, National Library of Medicine:
http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&orig_db=PubMed&cmd=current=Limits&pmfilter_Subsets=Complementary%20Medicine

modality is more conclusive, the provider's role is to ask about and document the use of IT, critically evaluate the evidence or lack of evidence, balance the potential risks with possible benefits, and assist the family in their decisions regarding use of integrative approaches for their child.

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