

Integrative Medicine in Childhood Cancer

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Abstract

The diagnosis of cancer in a child leaves parents and families devastated and vulnerable. In an effort to do everything possible, families often choose an integrative medicine approach to their child's care. Surveys have found that 31%–84% of children with cancer use complementary and alternative medicine and most often as supportive care agents. Several systematic reviews have demonstrated a clinical benefit for some select therapies; however, the safety and efficacy of the combination of biological therapies with conventional treatment remain largely unknown and garner concern due to the potential for interactions with conventional therapy. Given the sustained use and potential benefit of integrative medicine, additional research is warranted in pediatric oncology. Utilizing the available literature, clinical providers should aim to conduct open and nonjudgmental discussions with families about the use of integrative medicine so as to guide the safe integration of the two modalities.

Keywords: integrative medicine, nutrition, complementary/alternative medicine, pediatrics, cancer

Introduction

THE GLOBAL INCIDENCE of childhood cancer has observed a steady increase in the past decade likely due to increased access to treatment and improved reporting of childhood cancer.¹ Survival rates exceed 90% for the most common childhood malignancy, acute lymphoblastic leukemia (ALL), whereas overall survival of all pediatric malignancies is 70%.² The scientific advances for the treatment of childhood cancer have led to significant controversy over the use of understudied and less well-known treatments that comprise integrative medicine. Several surveys have reported that the combined use of integrative medicine in children undergoing treatment for malignancies is high in several countries^{3,4}; however, there is a general consensus that the evidence supporting its efficacy remains unclear for most indications. The lack of demonstrated safety and efficacy, the potential for adverse interactions with prescribed therapy, delays in seeking conventional treatment, and the risk of diminishing the high cure rate obtained for several pediatric malignancies have raised concerns about the use of integrative medicine and have created barriers to its integration into pediatric cancer care.^{5–8}

Nutritional Status and Dietary Intake in Pediatric Oncology

Nutrition is an integral component of supportive care in pediatric oncology with several studies demonstrating an associ-

ation between nutritional status, defined by anthropometric data, and outcome or toxicity in several pediatric malignancies. For example, a recent meta-analysis consisting of nearly 5000 children with leukemia found a significant association between nutritional status and outcome.⁹ In children with ALL, the most common childhood cancer, reduced survival was observed in children with higher body mass index (BMI) (relative risk [RR] 1.35, 95% confidence interval [CI] 1.20–1.51) than in those with lower BMI. In children with acute myelogenous leukemia, higher BMI was also significantly associated with poorer survival (RR 1.56, 95% CI 1.32–1.86) than lower BMI.⁹ Similar observations have been reported among children with solid tumors despite the heterogeneity of the data.

Remediation of poor nutritional status, both under- and overnutrition, appears to remove the adverse effects of nutritional status on toxicity and survival. A retrospective study exploring the effect of nutritional status at diagnosis and throughout therapy in children with ALL found that those who remained malnourished for the majority of treatment experienced increased toxicity and reduced survival, an effect that was not observed among those children who achieved normal classification of nutritional status.¹⁰ Similar observations have been reported in children residing in Central America.¹¹ These studies underscore the importance of timely and effective nutritional interventions.

The role of nutritional counseling in integrative oncology care for children with cancer is an understudied area.

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Counseling pediatric patients and families on comprehensive dietary plans is reflective of the underlying tenets in pediatric dietetics. The clinician should consider the complexity of the dietary regimen along with the required effort and any financial implications required to adopt the diet. In addition, the risks and benefits should be considered particularly in circumstances when excessive use of supplements or enemas is also recommended. The impact of the diet on socioeconomic factors, family structure, and overall quality of life should be weighed from the perspective of a child undergoing cancer therapy.¹² Counseling children and their families on healthy dietary patterns provides an opportunity for the clinician to empower children and adolescents to take an active role in their overall treatment. However, in some circumstances, dietary change may lead to increased stress and anxiety related to food, family conflicts, and inability to meet their daily nutrient requirements. Evaluation of each of these factors will improve the likelihood of the successful adoption of a nutritional plan that is embedded into a comprehensive integrative oncology prescription.

Specialized Diets

Neutropenic diet/low microbial diet

The neutropenic diet or low microbial diet is a component of conventional cancer care. With the increased attention of the beneficial effects of foods containing pre- and probiotics (refer to the Probiotics section), an appreciation for its history and underlying rationale is indicated when counseling a child with cancer.

Treatment for cancer often results in neutropenia (low white blood cell counts) that increases the risk of developing an infection. Food is an established vector of infections and it is presumed that neutropenia increases the risk of a food-borne illness especially in the setting of severe neutropenia (absolute neutrophil count <500 cells/mm³). The neutropenic diet or low microbial diet is frequently prescribed to minimize the risk of an infection through bacterial translocation by eliminating foods susceptible to infectious organisms. Although the scientific support for the neutropenic diet is largely empirical, adherence to these diets is difficult and provides further restraints on the individual's dietary intake.¹³ Most importantly, clinical trials have not found this diet to be effective in the prevention of infection over and above that of food safety guidelines.^{13–15} It is plausible that incorporating foods and supplements high in pre- or probiotics may be safe and beneficial within the context of childhood cancer; however, additional research is needed. It is essential that dietary counseling within integrative oncology adheres to food safety guidelines to reduce the risk of food-borne illnesses. A summary of food safety guidelines may be found at the United States Federal Drug Administration's website.

Ketogenic diet

The relationship between carbohydrates and cancer has been supported by preclinical experimental studies, prospective observational studies, and small pilot studies.¹⁶ The role of sugar in cancer growth is fostered from the early work of Otto Warburg who discovered that cancer cells

preferentially underwent glycolysis for energy production, even in the presence of oxygen,¹⁶ an observation that has become one of the most consistent hallmarks of cancer.¹⁷ The efficacy of the ketogenic diet among children and adolescents receiving cancer treatment has not been tested in a randomized trial. One case series described the administration of a ketogenic diet (60% medium chain triglycerides, 20% protein, 10% carbohydrate, and 10% dietary fat) for a period of 8 weeks to two children with astrocytoma.¹⁸ The authors found that the ketogenic diet promoted weight gain and improved quality of life, suggesting a beneficial effect among children with a brain tumor. Importantly, no adverse events were associated with the ketogenic diet. The ability of patients to adhere to a diet that is significantly different than typical dietary regimens may be difficult to test in a randomized study. Additional research evaluating its feasibility and effectiveness in childhood cancer is necessary before its incorporation into cancer care.

Lifestyle Interventions (Diet and Physical Activity)

Lifestyle interventions aimed at improving dietary intake and physical activity have a beneficial effect on reducing the risk of several adult cancers.¹⁹ Despite the high incidence of nutritional-related late effects among survivors of childhood cancer,^{20–22} there remains a paucity of data on the effect of lifestyle behaviors and risk of subsequent cancers or development of late effects. The clinical implications of unhealthy diets on the risk of cancer among adolescents are limited and focus primarily on dietary intake during adolescence and risk of breast cancer.²³ A limited number of dietary studies have evaluated single nutrients or food groups; few studies have reported on comprehensive indices of dietary intake (e.g., Healthy Eating Index).^{24,25} Moreover, the majority of studies have been observational rather than interventional studies. For physical activity, the existing studies have evaluated physical activity as an intervention during and after treatment.

In one of the largest observational dietary studies among survivors of childhood cancer, the diet of 170 survivors was evaluated. The authors found that improved adherence to national dietary guidelines was significantly associated with improved quality of life and reduced fatigue.²⁶ Moreover, this study identified at-risk groups of survivors who may be more vulnerable to the effects of suboptimal dietary practices. The authors observed that females, adolescence and young adults, and survivors of tumors of the central nervous system or lymphoma may be at higher risk of following poor dietary patterns than other groups of survivors. Tonorezos et al. reported that with greater adherence to the Mediterranean diet, the odds of developing metabolic syndrome fell by 31% (odds ratio 0.69; 95% CI 0.50–0.94; $p=0.019$),²⁷ lending preliminary support for the role of dietary behaviors for the prevention of late effects of childhood cancer. Other cross-sectional surveys have reported positive associations between adherence to dietary recommendations and a higher frequency of physical activity, suggesting that healthy dietary behaviors may also promote the adoption of other healthy lifestyle behaviors.²⁸

One study explored the effect of supplementation with and without dietary counseling on the bone density in survivors of

ALL.²⁹ Participants were randomized to nutritional counseling with or without supplementation that consisted of calcium and vitamin D for a 2-year period. The authors found that the addition of supplementation did not impart an added benefit over and above that of dietary counseling alone, suggesting that supplementation does not offset the benefits of comprehensive nutritional counseling. However, this study has several limitations including a wide age range reflecting different stages of bone maturation and a high drop-out rate, potentially introducing bias to the study findings.

Several studies have reported on physical activity in survivors of childhood cancer.³⁰ The percentage of participants who met national guidelines for physical activity ranged from 8%³¹ to 71%,³² but most of the studies reported that the majority of survivors did not meet recommended guidelines. Importantly, the prevalence of inactivity among survivors of cancer is higher than in the general population.³³ Compared with age-matched peers or healthy siblings, survivors consistently demonstrate lower levels of physical activity. In the largest descriptive study of physical activity ($N=9301$),³⁴ survivors were 20% less likely to meet Center for Disease Control guidelines for physical activity ($p<0.05$) and 60% less likely to report physical activity during the previous month than siblings ($p<0.05$). Finally, Phillips-Salimi et al. found that survivors ($n=651$) were less likely than controls to report any leisure-time activity in the past month ($p<0.05$).³⁵ Of the eight evaluated late effects, four may be moderated through effective lifestyle interventions.

Taken together, the limited data suggest that survivors of childhood cancer are not adhering to cancer prevention guidelines and are engaging in lifestyle behaviors that may further increase the risk for the development of nutrition-related chronic conditions such as heart disease, obesity, and metabolic syndrome. In most instances, survivor participation in healthy lifestyle behaviors is lower than in the general population. The finding that healthy dietary behaviors are associated with other healthy behaviors, such as physical activity, suggests that interventions targeting dietary strategies may positively impact other healthy behaviors among survivors potentially expanding the impact of dietary change on long-term health outcomes.

Nutritional Supplements

The use of nutritional supplements is one of the most controversial areas in integrative oncology care due to the potential interaction with conventional therapy. A recent systematic review of clinical trials evaluating the use of nutritional supplements for supportive care indications found several studies with a range of evidence.³⁶ The authors reported on 32 studies that investigated the use of dietary supplements for several supportive care indications, including mucositis ($N=12$),³⁷⁻⁴⁸ treatment-related toxicities ($N=5$),⁴⁹⁻⁵³ appetite and weight management ($N=3$),⁵⁴⁻⁵⁶ hepatic toxicity ($N=3$),⁵⁷⁻⁵⁹ fever and neutropenia ($N=3$),⁶⁰⁻⁶² neuropathy ($N=2$),^{63,64} chemotherapy-induced nausea and vomiting ($N=2$),^{65,66} bone mineral density ($N=1$),⁶⁷ and gastrointestinal symptoms ($N=1$).⁶⁸ Mixed, but encouraging, findings were reported for glutamine and honey for mucositis, zinc for the prevention of weight loss and infections, essential fatty acids for weight loss, and milk thistle for the treatment of hepatotoxicity.

Probiotics

Probiotic therapy is an emerging area of clinical practice and research in pediatric oncology. Several clinical studies in oncology have found that administration of cancer therapy has an adverse effect on the composition of the microbiome.⁶⁹ Concomitant exposure to prophylactic antibiotic therapy provides further insult to the microbiome. A pilot study performed on children undergoing hemopoietic stem cell transplantation (HSCT) found that administration of the probiotic, *Lactobacillus plantarum*, to be safe among this severely immune-compromised patient population.⁷⁰ Probiotic administration may be associated with reduced acute gastrointestinal graft-versus-host disease in HSCT.⁷⁰⁻⁷² However, the existing literature is not mature enough to recommend routine supplementation of probiotics at this time. Based on the existing literature, probiotic therapy may be beneficial for children with chronic diarrhea secondary to chemotherapy, abdominal radiation, prolonged antibiotic therapy, or *Clostridium difficile* infection.

Homeopathy

There have been trials investigating a single homeopathic agent in pediatric oncology. TRAUMEEL S[®] is a homeopathic remedy that contains extracts from several plants and minerals, all of them highly diluted (10-1-10-9 of the stock solution).⁴¹ TRAUMEEL S has been investigated in both a small pilot study and large randomized clinical trial with conflicting results. TRAUMEEL S was administered to 32 pediatric patients undergoing a bone marrow transplant and was associated with significant reductions in the severity and duration of stomatitis ($p<0.01$).⁴¹ No adverse events were reported. However, a double-blind randomized trial conducted through the Children's Oncology Group in patients undergoing myeloablative stem cell transplantation did not find a benefit with the administration of TRAUMEEL S.⁴³ The study found no statistical difference in incidence or severity of mucositis in the TRAUMEEL S group compared with placebo. However, adherence to 100% of the days was poor, adherence was 37% and 35% in the TRAUMEEL S and placebo groups, respectively. A trend toward less narcotic usage for the management of mucositis was observed in the TRAUMEEL S patients. It is unknown whether fewer administrations delivering the same dose of TRAUMEEL S would have improved adherence.

Complementary Therapies

Acupuncture

A white paper published by the National Cancer Institute presented the evidence on the role of acupuncture in cancer care.⁷³ Overall, acupuncture appears to be safe in the context of cancer care, even in the pediatric population. A safety study performed in children and adolescents undergoing chemotherapy including stem cell transplantation found that acupuncture was safe among those with severe thrombocytopenia.^{74,75} Although limited in pediatrics, two clinical studies have evaluated the role of acupuncture for the prevention/treatment of chemotherapy-induced nausea and vomiting.^{76,77} Each study reported a significant decline in the use of antiemetics. One study reported a significant decrease in episodes of retching and/or vomiting.⁷⁷

Aromatherapy

One good quality study investigated aromatherapy among children undergoing HSCT.⁷⁸ This trial examined the effects of bergamot essential oil on anxiety in 27 children undergoing HSCT for a variety of diagnoses. The authors found increased nausea and anxiety in the aromatherapy group than in the control group.

Massage

Massage therapy is a supportive care treatment that can be readily applied, either by credentialed massage therapists or by parents who have learned massage techniques with a licensed therapist. Parents of children with cancer and adults with cancer have consistently reported that massage therapy provides benefit during anticancer therapy. There have been several studies evaluating the efficacy of massage therapy in the setting of pediatric oncology.³⁶ The available evidence suggests that massage therapy may be beneficial for several symptoms, which concurs with a recent consensus statement on nonpharmacologic approaches.⁷⁹ Evidence-based nonpharmacologic massage therapy may be a cost-effective approach to advance the provision of supportive care throughout the spectrum of pediatric cancer care.

Summary

There remains a significant interest in approaching pediatric cancer care from an integrative perspective, especially for symptom management. Despite sustained interest among conventional practitioners in researching promising integrative therapies, such as acupuncture and massage, there is insufficient evidence to guide most discussions related to nutritional or biological therapies during conventional treatment. However, some integrative therapies, such as acupuncture and massage, are beneficial and have little risk of interfering with conventional treatment or increasing the risk of an adverse event. The International Society of Pediatric Oncology developed guidelines to guide the assimilation of integrative oncology into cancer care, including open non-judgmental discussions with families and the need for bidirectional educational opportunities.⁸⁰ The authors advocate for more research as this will pave the way for integration of the two medicinal approaches into pediatric cancer care.

Author Disclosure Statement

No competing financial interests exist.

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