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Complementary and Alternative Medicine (CAM) Use in Pediatric Oncology: A new horizon or costly myth?

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Context: Complementary and alternative medicines (CAMs) are increasingly being utilized in the pediatric cancer population, despite unproven risks and benefits, and significant additional cost of treatment.

Objective: To identify the prevalence of CAM use and the most frequently utilized CAMs, and to examine the physiologic impact of CAM in pediatric cancer patients undergoing chemotherapy. Additional objectives included identifying the cost associated with CAM, and the rationale for CAM usage.

Design: Cross-sectional study of 40 children, between 2 to 18, diagnosed with a malignancy of any kind between 2000 and 2008. Families completed a survey, including questions on demographics, utilization of CAMs, and any associated costs. Chart review was performed and Absolute Neutrophil Count (ANC) was trended during CAM use. Categorical data were analyzed using a Pearson’s Chi-square test with Fischer Exact Test. Student’s t test was performed to evaluate association between CAM and ANC.

Results: The prevalence of CAM usage in our population was 54%. Patients frequently used anti-oxidant vitamins and minerals for prevention of further illness 72.7% (p=0.001), and frequently used herbs and herbal teas for relief from treatment-related symptoms 83.3% (p=0.004). Lower ANCs were found in patients using immune modulating juices (ANC average 1542, p=0.025) when compared to all other groups. Finally, 70% of patients and families spent between $25-120/month on CAM treatment.

Conclusion: CAM use is prevalent among pediatric cancer patients and is used primarily for alleviation of treatment related side-effects and augmentation of immune status. However, there is considerable cost associated with treatment, and some therapies may be associated with lower absolute neutrophil counts during treatment.
Introduction

Complementary and alternative medicines (CAM) have been increasingly utilized in the treatment of children with cancer during the past three decades.\textsuperscript{1,2,3,4,5} CAMs encompass broad treatment categories, ranging from ingested botanical agents, to massage and acupuncture, and even include prayer and spiritual practices.\textsuperscript{6,7} By definition, CAMs have scientifically unproven risks and benefits, yet patients are compelled to use them for a multitude of reasons.\textsuperscript{8,9} Several factors make CAM use compelling. CAMs carry the designation of being derived from a ‘natural’ substance, and consequently are assumed to be safe.\textsuperscript{2} Many CAMs are far less expensive than FDA-approved drugs, do not require a prescription, and therefore offer patients a greater degree of autonomy in using them for treatment effects. When a child is faced with cancer, parents sometimes provide CAMs to their children with the justification that ‘everything possible is being done’ to achieve a cure for their child.\textsuperscript{10,11} Not surprisingly, many patients and their families utilize CAMs but do not disclose CAM usage to their physician, because they perceive that these therapies are not ‘drugs’ or because they fear reproach from healthcare personnel because such practices may be viewed as a form of non-compliance.\textsuperscript{6,12} Nevertheless, many CAMs have pharmacobiological activities that may cause serious adverse drug events or drug-drug interactions.

Despite the abundance of available CAM therapies and the prevalence of CAM usage, CAM therapies are not well regulated. Concentrations of active ingredients can vary greatly from product to product, a practice that can obscure the true incidence of specific side-effects.\textsuperscript{13} While most CAMs are not associated with toxicities, several have
been associated with serious adverse events that have lead to bleeding disorders, hypertensive crisis, and coronary ischemia. Even simple herbal infusions have been linked to fatal gastroenteric, hepatic, and nephrotoxic episodes.\textsuperscript{14,15,16} Other herbal preparations contain high levels of contaminants such heavy metals, fungus, and bacteria.\textsuperscript{17,18} Less obvious to the cancer patient are instances where CAMs may result in up-regulation of CYP3A4, resulting in chemotherapy inactivation, or may enhance the expression of ATPase Binding Cassette (ABC) protein-mediated drug efflux, leading to reduced anti-cancer effects.\textsuperscript{19,20,21,22,23}

Recent investigations have shown that anti-oxidant supplements can attenuate the cytotoxic effects of cyclophosphamide, vincristine, methotrexate, and cytarabine; drugs which derive at least part of their effect by generating reactive oxygen species.\textsuperscript{24} Used in conjunction with these agents, high-dose vitamins, minerals, and related CAMs may limit the ability of drugs that are commonly used to treat pediatric malignancies.\textsuperscript{25} By reducing the effectiveness of cytotoxic therapy against cancer cells, these CAMs may lead, in theory, to relapse as a serious adverse event.\textsuperscript{26,27,28,29,30,31} On the other hand, CAMs that diminish myelosuppresion, mucositis, and chemotherapy-associated cachexia might enhance a patient’s compliance with FDA-approved chemotherapeutic agents.

A number of studies have assessed CAM use in children with cancer, and have shown that despite the prevalence of CAM use in the pediatric cancer population, it is still unclear whether these therapies deserve a place in the treatment of cancer.\textsuperscript{32} This fact is important when considered alongside of the economic burdens associated with CAM use, which may total up to $250/year for therapies which may have limited or even
deleterious impact on overall disease course.\textsuperscript{33,34} While a number of studies have provided important insights into the use of CAMs for children receiving chemotherapy, it remains unclear whether correlations exist between chemotherapy-associated toxicities and specific CAM selection, precise costs associated with CAM use, or whether CAM usage might impact hematopoietic function. To address these concerns, we performed a cross-sectional survey of a population of patients at the University of New Mexico. We found that CAMs were frequently utilized in our pediatric cancer population, and were associated with a significant impact on a number of biological and economic outcomes associated with a cancer treatment course.

**Patients and Methods and Survey Instrument**

We performed a cross-sectional study of 40 children and young adults who were between the ages of 2-19 and diagnosed with a malignancy of any kind between 2000 and 2008. Inclusion criteria included the provision of written, informed consent in accordance of institutional guidelines (HRRC #07-131) and had a parent who could read/speak English, or who could themselves (if 17 years of age or older) read/speak English. Patients were treated on a variety of studies sponsored by the Children’s Oncology Group, or as supported in the written literature as best clinical practice. Study participants received cancer treatment for a minimum of 8 weeks before being recruited for participation in a short survey (see Appendix I). Our 10 question survey included questions regarding demographic data, utilization of CAM, and in relevant patients, the costs associated with CAM use. For the purposes of a chart review, all patients were assigned a unique identification number.
Stratification and Chart Review

Data were stratified based on reported CAM usage (use vs. non-use), type of cancer, and age (0-4 yrs, 5-11 yrs, 12-18 yrs) if applicable. For correlative purposes, in patients having acute lymphoblastic leukemia, all annotated data was correlated with mean absolute neutrophil counts (ANC) during maintenance phase of therapy. In order to adjust for differences in age, diagnosis/stage, and use of cytokine stimulation, the ANC was recorded for each patient at the start of treatment then every two weeks until the first 8 weeks of chemotherapy had been completed. Subsequently, data from patients who continued to receive cytokine treatment was collected on a monthly basis ± 2 days until the end of treatment.

Statistical Methods and Data Analysis

To facilitate uniform statistical interpretation the study team created five categorical designations into which each CAM Therapy could be assigned (Table 1). The categories were based upon 1) type of modality and 2) proposed mechanism of action of that therapy. Statistical analyses were performed to compare prevalence of CAM use according to type of modality. Categorical data were analyzed using a Pearson’s Chi-square test with Fischer Exact Test for data sets where 1/5th or more of the cells of a table were sparsely populated (cell value < 5). Alpha was set at $P \leq 0.05$. Likewise, Pearson Chi-square test was used to evaluate potential associations between Reasons for Use and Costs. To evaluate relationships between CAM usage according to age and the Absolute Neutrophil Count (ANC), Student’s t test were performed.
Results

Over the course of 18 months, we identified 40 patients who responded to our survey questionnaire. Among the patients studied, 62% were boys and 38% were girls who were affected by a variety of cancers (Table 1). Ages ranged from 2 to 18 years of age. Based on responses to the survey, questions, 39 were eligible for complete analysis. Four of the 39 patients did not complete the sections of the survey specifying type of CAM modality and associated costs, and were therefore excluded from those respective portions of the data analysis. The remaining 35 were eligible for Absolute Neutrophil Count (ANC) comparison based upon 1) assenting to ANC review and 2) presence of complete medical records.

Approximately 54% of all respondents reported CAM use during at least a one-month period during their cancer treatment. As a consequence of our finding, a high prevalence of CAM usage in our patient population, we next investigated which substances were most commonly used and the justifications for their use (Figure 1). Multiple respondents (n=6) used more than one CAM modality. In these instances, we analyzed multiple CAM exposures as separate incidences. The most frequently cited reasons for CAM use by patients, in descending order of occurrence, were to prevent further illness, to relieve treatment-related toxicities, and to provide relief from cancer-related symptoms.

Our survey results revealed that most botanical CAMs possessed known antioxidant effects. In addition, a number of respondents cited using minerals, immune
modulating juices, herbs and herbal teas, which have also been reported to have anti-
oxidant effects.\textsuperscript{24-31} Therefore, we next sought to identify potential correlations linking
botanical CAM agents with the reasons why patients used them. We found statistically
significant correlations between anti-oxidant vitamin and mineral use in patients who
used this class of CAM for the relief of treatment-related symptoms (Chi-Square Test
\( p=0.041 \)) and for prevention of further illness (\( p=0.001 \); Table 3). Furthermore, we found
that the use of herbs and herbal teas were strongly correlated with our respondents
who used CAMs to relieve cancer-treatment related symptoms (\( p=0.004 \)). Among the
CAMs identified in our survey, we found a trend among respondents to utilize herbs and
herbal teas to alleviate cancer-related symptoms. Moreover, we note a trend to use
immune-modulating juices to prevent further illness (\( p=0.063 \)). We found no statistical
correlation with regard to use of CAM for specific cancer diagnosis or with age.

CAMs have been predicted to neutralize the effects of anti-cancer therapy, and
therefore in theory might increase the risk of relapse. Based on the investigations of
Weijl et al. and others, we hypothesized that CAM would rescue patients from the
effects of anti-metabolite-based therapy directed against ALL and other pediatric
cancers. while there were clear statistical associations between reason for use and
selection of CAM modality, there was no statistical correlation demonstrated with
regard to use of CAM based upon the type of cancer diagnosis, i.e. leukemia and
lymphoma vs. all soft-tissue tumors. Moreover, there was no statistical correlation with
regard to the subtype of CAM and diagnosis. Finally, there was no statistical correlation
with regard to age and use of a CAM, nor subtype of CAM modalities and age set (grouped as 0-4, 5-11, 12-18 years of age).

Based on the investigations of Weijl et al. and others, we hypothesized that CAM would increase Absolute Neutrophil Counts in pediatric cancer patients due to the rescuing effects of anti-oxidants.\textsuperscript{24-26} We collected data related to ANC in CAM and non-CAM users, as the neutrophil count is used to intensify or de-intensify therapy in the maintenance phase of a number of ALL studies. While we found no statistical difference in ANCs between CAM users and non-users, we found a trend between low ANC and the utilization of immune-modulating juices in our respondents who used CAMs.

To better understand the economic burden of CAM usage, we next assessed costs associated with their use. We found 23.5\% reported spending between $1-5 per week, 32.5\% spent between $6-10 per week, 17.6\% spent between $21-30 per week, and another 23.5\% reported spending in excess of $30 per week. Among specific subcategories of CAM users, 72.6\% of those utilizing Anti-Oxidants and Minerals spent between $6-20 each week. For patients and their families using immune modulating juices, 66.6\% reported spending >$30 each week. Despite these costs, 21 of 27 respondents (77.7\%) indicated an interest in learning more about CAM. These responses were often accompanied by personal annotations suggesting an interest in the topic (see Discussion). Interestingly, 38\% of respondents who wished to learn more about CAMs reported that they had not used CAMs in treatment of themselves/their child during cancer treatment course.
Discussion

Dose-intensified multi-agent therapy has achieved considerable increases in survival rates for children and young adults who are treated for cancer. While often forgotten or not assessed, patients and their families often rely upon CAMs to help them through a treatment course.\textsuperscript{3-8,10} Because of the frequency which CAM use has previously been demonstrated, and because CAMs can affect chemotherapy, we assessed CAM usage in a single-institution study. In our survey of 40 patients, we found that CAM was utilized by over half of our respondents. We discovered that patients and their families utilized anti-oxidants, vitamins and minerals, and herbs/herbal infusions to control treatment-related symptoms and to prevent additional treatment-related toxicities. Despite the unproven risks and benefits of CAMs, we also found that patients and their families were willing to spend more than $500 annually for these products. We were surprised to find that, in contrast to our initial hypothesis, patients using immune modulating juices had a comparatively lower mean ANC than non-CAM users when receiving maintenance treatment for childhood cancer. Our results call for further investigation into the use, patient/parental justification, and biological effects of CAM among children and young adults who face a cancer diagnosis.

We found that more than half of our patients reported using CAMs in one form or another. In agreement with our results, Sencer, Kelly, and others\textsuperscript{3-5} reported CAM usage between 36 and 84\% in their studies of pediatric cancer patients.

We found that Anti-Oxidant Vitamins and Minerals and Herbs and Herbal Teas were used most frequently in childhood cancer patients. Our results differed from the
results of Post-White et al. who reported that the prayer was the most frequently used modality in this population (69.4%) followed by massage, vitamins, and supplement use. The primary reasons for CAM utilization in our study were for the relief of treatment-related symptoms as well as prevention of additional toxicities. While other studies including that of Post-White have similarly found that the primary reason for CAM use was to manage side effects, secondary reasons for CAM use in other studies included feeling more hopeful and coping with emotional effects of cancer. Our results suggest that patients and families are using CAM not to treat cancer itself, nor to bolster emotional well-being, but to ameliorate the various side-effects of chemotherapy and to mitigate the risk of neutropenic illness.

The most interesting finding of this study was the impact of CAM on absolute neutrophil count. We had originally hypothesized that CAM would rescue the effects of chemotherapy, thereby increasing ANC. In contrast, we found that those using immune-modulating juices had lower mean ANCs when compared to both non-CAM users and all other CAM users (Table 3). The difference in absolute neutrophil count (<1.0x10^3) does not appear clinically significant; however this can’t be substantiated without longitudinal data collection. We hypothesize that this correlation may reflect that this patient subset initially had low ANCs. Given relatively low ANC values, families may have elected to seek alternative methods for boosting neutrophil counts to help their children avoid neutropenic illness. This hypothesis is corroborated by the fact that these patients were more likely to use immune-modulating juices to prevent further illness (Table 3). Among other CAM categories, there was no significant difference in ANC when
compared with non-CAM users. These data suggest that the medical community should seek to identify how complementary and alternative medicines may interact with chemotherapeutic regimens.

Cost associated with CAM use was similar to that noted by Kligler, Sapna, Alsawaf, and Jatoi, however when data were extrapolated over the course of a year or over the course of treatment, costs were substantially higher.35 The specific types of CAM utilized and the reasons for utilization were different from those reported by Post-White et al. and Cheung et al.35,36 Our results suggest further investigation into the role of CAM as an adjunctive treatment in cancer. We next investigated the cost associated with CAM usage. We demonstrated that 76.5% of patients who use CAMs can spend between $24 and $100+ a month. This average is more than twice the mean of $27 previously suggested Alsawaf and Jatoi. When our data is extrapolated over the course of one year, patients may spend between $300 and $1500. If families elect to use the same CAM throughout the duration of treatment, some families may spend close to $4000 for complementary and alternative therapies. These data are significant given the prevalence, cost, and unknown effects of CAM use. Further study is warranted to assess the cost/benefit outcomes in of CAM use childhood cancer patients over the course of treatment. An overwhelming three-quarters of patients or patients’ families wanted more information on CAM, even if they denied current CAM use. Among the subjective responses of patients and families were:

I’m glad this study is happening.

We would want to see more CAM added to chemo regimens.
What [other] therapies could be used?

I hope in the future that CAM will be part of the Chemo treatment.

Future Directions

Complementary therapies are frequently being utilized in the treatment of cancer despite the high cost associated with these therapies. Moreover, CAM seems to have a physiologically important role in cancer patients. Therefore, future investigations would be invaluable in establishing: 1) What impact CAM has on cancer and cancer treatment? 2) Does the use of immune modulating juices impact hematopoiesis resulting in lower ANCs or are these juices harmless but costly adjunctive treatments? Finally, because CAM use 1) is prevalent 2) is frequently not disclosed to physicians and 3) possibly mitigates chemotherapeutic treatment, is CAM use a form of non-compliance?

Secondly, Spanish-speaking only families were not approached for participation in the study, primarily because the researchers could not have the survey or consent forms translated in time, nor could researchers explain, in full-detail the purpose and extent of the study. The exclusion of this population may have artificially decreased reported CAM usage, as these patients often use traditional folk practices including usage of alternative medicines from curanderos (healers) and yerberos (herbalists) alongside of traditional medical practices. In a study conducted in South Texas, with a population demographic similar to that in this metropolitan area, 58% of surveyed adult patients who use CAM.\textsuperscript{37,38} It would be beneficial to include this patient population in the future to fully assess 1) what percentage of this population is using CAM 2) what CAMs this population is using and 3) if they are different from mainstream CAMs.
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