Supportive Naturopathic Management of Long-Term Effects of Acute Lymphoblastic Leukemia Treatment

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With the number of childhood cancer survivors rising steadily each year,[1] it is important that physicians are adept at managing long-term sequelae of treatment.[2] Advances in cancer treatments have significantly increased childhood cancer survival rates since the 1970's.[1,3] Recent research estimates that 67% of childhood cancer survivors will develop at least one late-onset treatment related adverse effect and in 25% of survivors that side effect may be life-threatening.[2] Leukemia is the most commonly diagnosed childhood cancer (32% of all cases), specifically acute lymphocytic leukemia (ALL), which most commonly occurs before the age of five.[1,3] This article will discuss the importance of monitoring long-term sequelae from the treat-ment of survivors of ALL and review current literature on safe and effective naturopathic interventions for managing side effects of conven-tional ALL treatment and potential long-term complications.

Health problems occurring months to years after cancer treatment are termed "late effects." Late effects are dependent upon the primary malignancy and its corresponding treatment.[4] Importantly, the incidence of late effects increases over time. Reducing acute side effects while undergoing treatment may help minimize late effects or potentially reduce incidence rates. Regular follow-up assessment and management is central to monitoring and treating late effects and can provide a better overall outcome and quality of life. Education surrounding healthy habits of diet and exercise for survivors is a primary component of supporting patients.

Current survivorship guidelines published by the Children's Oncology Group for Long-Term Follow-Up of Childhood, Adolescent and Young Adult Cancers serves as a resource for healthcare professionals working with survivors. The guidelines are intended to help support a better quality of life and minimize complication-related health care costs for pediatric cancer survivors.[5] These guidelines also provide standardized follow-up care with the goals of:

a) Promoting a healthy lifestyle

b) Providing ongoing monitoring

c) Facilitating early identification of late effects

d) Providing timely intervention for late effects[5]

These guidelines are not meant to provide follow-up for the survivor's primary malignancy. Patients are assumed to be asymptomatic and healthcare professionals who do not regularly care for survivors of pediatric cancers are encouraged to seek out care from a pediatric oncology long-term follow up center.[5] The guidelines were initially released in 2002 and are updated with current literature at least every 5 years.

The Children's Oncology Group lists potential harms of the guidelines as, "increased patient anxiety related to enhanced awareness of possible complications as well as potential false-positive screenings" leading to unnecessary further testing.[5] Informed consent and individualized guidelines based on clinical judgement is expected within the context of these guidelines as well.[5]

Guidelines for monitoring late effects of *any* cancer treatment (Table 1) include screening for mental health disorders, risky behaviours, psychosocial disabilities due to pain, adverse psychosocial/quality of life effects, dental abnormalities, limitations in access to health care and insurance as well as fatigue and sleep problems.[5]

Recent statistics estimate that 985 Canadian children, aged 0 to 14 years, are diagnosed with ALL each year.[6] Based on the most common treatment protocols outlined below, the guidelines can be utilized to provide better quality of life to the patient and monitoring of late effects.

The most common treatment for children with ALL is chemotherapy, which is provided in 3 phases:

1. Induction
2. Consolidation (also called intensification)
3. Maintenance[7]

TABLE 1: Common Late Effects Associated with Cancer Treatment

LATE EFFECT	ASSESSMENT	CONVENTIONAL THERAPIES
Mental Health Disorders • Depression • Anxiety • PTSD • Suicidal Ideation	Annual Screening	• Psychological consultation in patients with emotional difficulties related to cancer experience including physical deformities or chronic disabilities[5] • Appropriate psychotropic medications[5] • Evaluation of parent of PTSD[5]
Risky Behaviors Behaviors known to increase likelihood of subsequent illness of injury • Smoking • Underage or excessive drinking • Drug use • Eating disorders • Sedentary lifestyle • Unprotected sex • Excessive UV radiation exposure	Annual Screening	• Smokefree.gov[5] • Cancer.org/healthy/stay-away-from-tobacco[5] • Cognitive Behavioural Therapy
Psychosocial Disabilities due to pain	Annual Screening	• Psychological consultation in patient with chronic pain[5] • Appropriate psychotropic medications[5] • Referral to pain rehabilitation clinic[5]
Adverse Psychosocial / QoL Effects • Social Withdrawal • Educational problems • Relational problems • Underemployment / Unemployment • Dependent Living	Annual Screening	• Psychological consultation in patients with emotional difficulties related to cancer experience including physical deformities or chronic disabilities[5] • Social work consultation[5] • Refer as indicated to school liaison in community or cancer center (psychologist, Social worker, school counselor) to facilitate acquisition of education or vocational services[5] • Refer as indicated for neuropsychological evaluation[5]
Dental Abnormalities	Annual Oral Exam, Dental Exam and Cleaning every six months	• Regular dental care including fluoride applications[5] • Baseline panorex prior to dental procedure to evaluate root development[5]
Limitations in Health Care Assess and Insurance		• Social work consultation[5]
Fatigue and Sleep Problems	Annual Psychosocial Assessment	• Screen for physical sources of fatigue such as anemia, sleep disturbances, nutritional deficiencies, cardiomyopathy, pulmonary fibrosis, hypothyroidism or other endocrinopathy[5] • Referral to specialties such as endocrinology, sleep lab / study, or nutrition as needed[5] • Referral to psychology for behavioral intervention for emotional difficulties contributing to sleep and fatigue[5]

The duration of treatment is typically 2 years for girls and 3 years for boys, with the most intense treatment being in the initial induction phase.[7] Children with ALL are often classified by risk groups to ensure the correct types of chemotherapeutic drugs and doses are given.[7] The treatment groups are divided into the following three groups: Standard Treatment for uncomplicated ALL, High Risk, or patients that are positive for the Philadelphia Chromosome. Depending on which risk group a patient is placed in, treatment can be more or less intense with the Philadelphia Chromosome group receiving the most intense treatment.[7]

More than 95% of children with ALL enter remission after one month of induction treatment.[7] The next, and usually more intense, consolidation phase of chemo starts once the leukemia is in remission and typically lasts for several months (Table 3).[7]

If the leukemia remains in remission after induction and consolidation then maintenance therapy is initiated (Table 4). Higher risk patients may receive more intense maintenance chemotherapy and intrathecal therapy.[7]

TABLE 2: Induction Phase Treatment of Children with Acute Lymphocytic Leukemia (ALL)

INDUCTION PHASE	ALL STANDARD TREATMENT	HIGH RISK GROUP	PHILADELPHIA CHROMOSOME (+)	LATE EFFECTS DUE TO TREATMENT
Drugs	• L-asparaginase • Vincristine • Dexamethasone	Add: • Daunorubicin (anthracycline) Possible • Methotrexate and/or 6-mercaptopurine	Add: • Imatinib (Gleevec)	**L-asparaginase** - no known late effects[5] **Vincristine** - peripheral sensory or motor neuropathy, vasospastic attacks (Raynaud's phenomenon), increased risk of skin cancer (10 years post treatment)[5] **Dexamethasone** - Decreased Bone Mineral Density, Osteonecrosis (avascular necrosis), cataracts[5] **Daunorubicin (anthracycline)** - Heart failure (more likely at dosages above 250 mg/meter squared)[10] **6-mercaptopurine** - Hepatic dysfunction[5] **Imatinib (Gleevec)** - Further Study needed[8]
Intrathecal Chemotherapy	Methotrexate	Add • Hydrocortisone • Cytarabine (ara-C)		**Methotrexate** - Hepatic dysfunction, Neurocognitive deficits, Clinical leukoencephalopathy[5] **Cytarabine (ara-C)** - cognition, learning and memory difficulties, reduced fertility or infertility in men and women, Hepatic dysfunction[9]
Radiation		May be given radiation therapy to brain although not as common.[7]		Delayed cognitive ability and growth even at small doses, metabolic syndrome.[7] Stroke and osteonecrosis[13] Second cancers[16]

TABLE 3: Consolidation Phase of ALL Treatment

CONSOLIDATION PHASE	ALL STANDARD TREATMENT	HIGH RISK GROUP	PHILADELPHIA CHROMOSOME (+)	LATE EFFECTS DUE TO TREATMENT
Drugs	Regimen differs among cancer centers • Methotrexate 6-mercaptopurine (6-MP) • Vincristine • L-asparaginase and/or prednisone	Add: • L-asparaginase • Doxorubicin • Etoposide • Cyclophosphamide • Cytarabine (ara-C) • Dexamethasone is substituted for prednisone	Add: • Imatinib (Gleevec)	**Doxorubicin** - cardiovascular damage and dysfunction, secondary cancers.[5] **Etoposide** - increased risk for myelodysplastic syndrome and acute myeloid leukemia.[5] **Cyclophosphamide** - increased risk for myelodysplastic sy ndrome and acute myeloid leukemia, hepatic dysfunction, increased risk for bladder cancer (10 years post treatment).[5] **Cytarabine** - see above **Methotrexate, mercaptopurine, vincristine, L-asparaginase, prednisone** - see above
Intrathecal Chemotherapy	Continued intrathecal chemotherapy	Continued intrathecal chemotherapy May require second round of chemotherapy treatment	Continued intrathecal chemotherapy	**Methotrexate** - Hepatic dysfunction, Neurocognitive deficits, Clinical leukoencephalopathy[5] **Cytarabine (ara-C)** - cognition, learning and memory difficulties, reduced fertility or infertility in men and women, hepatic dysfunction[9]
Stem Cell Transplant		Optional Stem Cell Transplant especially if sibling is a match		Hepatic dysfunction[5]

TABLE 4: Maintenance Phase of ALL

DRUGS	LATE EFFECTS DUE TO CANCER TREATMENT
Daily: 6-mercaptopurine (6-MP)	6-mercaptopurine - see above
Weekly: methotrexate often along with vincristine (IV)	Methotrexate – see above. Vincristine – see above
Steroid (prednisone or dexamethasone) • Given for brief period every 4-8 weeks	Prednisone or dexamethasone - see above

Supportive naturopathic treatment options for ALL patients

ALL is the most common pediatric cancer.[11] Due to improved therapies, the five year survival rate for children with ALL is nearly 90%.[11] However, 67% of those develop at least one treatment-related late effect. The severity and intensity of these late effects is largely dependent on the type of treatment received (i.e. chemotherapy, radiation, immunotherapy).[11] Adult survivors of pediatric cancer are more prone to chronic illness and have an 80.5% risk of having at least one disabling or life-threatening condition by the age of 45.[12] The most common late effects observed in ALL survivors is cardiovascular disease, peripheral or sensory neuropathy, bladder and skin cancers (10 years post-treatment), decreased bone mineral density, cognitive learning and memory difficulties, obesity, dental abnormalities, and fatigue and sleep problems.[5] Monitoring for mental health disorders should also be considered along with limitations in health care access and insurance.[5]

Naturopathic medicine utilizes individualized patient-centered care. Treatment and follow-up care will differ depending on the patient's age, specific conventional therapies, personal medical history, as well as the side effects they experienced as a result of conventional treatment. Following the conclusion of their conventional cancer treatment, patients should have an annual thorough physical exam and medical history intake. This visit should incorporate pertinent bloodwork and imaging.[4,13] Patients should also be monitored for the following: any previous health concerns before the cancer diagnosis, organ and tissue damage, changes in bodily function from the cancer or its treatment, developmental abnormalities, mood changes, abnormal behavioral changes, learning disabilities, nutritional status and any second cancers.[4,13] ALL survivors should be counselled on nutrition, exercise, maintaining a healthy weight and encouraging as well as monitoring regular dental appointments.[4,13]

The role of naturopathic medicine within oncology has grown in recent years. The Oncology Association of Naturopathic Physicians (OncANP) was formed in 2004 with the goal to improve survival and quality of life for cancer patients.[14] In 2016, the OncANP developed a Principles of Care (POC) guideline to help provide patient-centered care within the areas of assessment, treatment planning, care management, interprofessional collaboration, and survivorship care.[14] There have also been significant advances in published research demonstrating the safety and efficacy of natural and supportive care.[14]

In keeping with the POC guidelines, the care management for survivors of ALL should incorporate best-practice recommendations supported by evidence-based research and include the totality of the patient's circumstances.[14] The patient's personal preferences and values are discussed while ensuring appropriate referrals are recommended as needed.

Of long-term survivors, 90% report receiving some form of medical care for treatment related adverse effects, of which only 18% receive screening tests or counselling, which may help to reduce their specific risks of cancer.[15] This highlights the need for naturopathic medicine. Promoting healthy lifestyle behaviors with a focus on diet and physical activity for the ALL survivor helps to mitigate or prevent late-term effects.[15] Adult survivors of ALL are at an increased risk of obesity, dyslipidemia, hypertension and insulin resistance. This may lead to earlier onset cardiovascular disease, which is the leading cause of non-relapse deaths in survivors of childhood cancer.[16] Early intervention to alter body composition, in order to maintain a healthy BMI and decrease insulin resistance, may contribute significantly to decreasing the risk of premature morbidity and mortality.[16] It is important to follow proper screening guidelines in order to prevent cardiovascular disease in high risk pediatric ALL survivors, including referrals for ECG's and testing for biomarkers.[17]

Decreased physical activity levels among ALL pediatric survivors have been linked to the development of metabolic syndrome.[18] A recent meta-analysis showed that obesity is prevalent in ALL survivors, independent of patient characteristics and treatment approaches.[18] Disorders of the skeletal, musculoskeletal, neuromuscular, cardiopulmonary and cardiovascular systems, as well as metabolic disorders are all reported to be positively impacted by a number of different studies ranging from 3 weeks to 12 months.[19] Counselling pediatric ALL survivors on increasing their physical activity may be beneficial as a part of their naturopathic treatment plan with the above disorders.

Diet and nutrition may play an important role when it comes to reducing the risk of developing secondary malignancies and cardiovascular disease.[20,21,22] For pediatric ALL survivors, educating patients and parents on evidence-based nutritional protocols is crucial for their long-term health in preventing post-treatment obesity.[20,23] An example of an evidence based approach to nutrition in this case is the Mediterranean diet. This nutritional protocol consists of high amounts of diverse vegetables and fruit, nuts, seeds, poultry and fish, uses olive oil as a fat source, and recommends limiting red meat and processed food.[21,22] It also promotes a balanced ratio of omega 6 and omega 3 fatty acids, high fibre and antioxidant intake.[21,22] The NOURISH-T study by Stern et al. demonstrated benefits when pediatric cancer survivors consumed a diet high in vegetables and fruit as well as whole grains along with avoiding foods high in fat.[23]

Naturopathic doctors should also counsel pediatric ALL survivors to minimize the risk of comorbidities and ALL recurrence.[4] These behaviors include smoking, excessive alcohol intake, drug use, excessive UV radiation exposure and a sedentary lifestyle.[4,24] Increased frequency of follow up appointments may be necessary to support patients who have already engaged in these unhealthy habits.[25]

Bone mineral density (BMD) is also a long term concern for survivors of pediatric cancer.[5,12,19,26] A 2013 report from the St. Jude Lifetime Cohort Study discovered that approximately 10% of young adult pediatric cancer survivors whose conventional

cancer therapy included dexamethasone and methotrexate developed osteoporosis.[5,12,26] Male patients and those who received conventional cancer treatment during adolescence are at higher risk of low BMD.[26] It is important to follow appropriate screening guidelines, which include bone density evaluation (DXA) in order to avoid low BMD.[27] Vitamin D and calcium supplementation, as well as weight-bearing exercises used to increase lean muscle mass, may help increase BMD in pediatric cancer survivors.[26]

Vitamin D deficiency is common in pediatric ALL patients and supplementation may improve this deficiency within a short period of time.[27] Protection from UV exposure to help prevent skin cancer, which is a long-term risk factor for patients who had vincristine chemotherapy, may contribute to the development of vitamin D deficiency.[5] Low serum vitamin D levels are associated with developing secondary cancers, cardiovascular disease as well as low BMD in ALL survivors.[28,29] A 2017 study by Demirsoy et al. demonstrated that patients who were not supplemented with vitamin D or calcium had the lowest BMD scores at 8 and 24 months post-diagnosis; therefore, supplementation with vitamin D and calcium is important for long term prevention and treatment of low BMD.[30]

The risk of secondary effects increases with increasing age of the adult survivor as well.[31] Follow up care should be initiated early and throughout their lifetime. In the Childhood Cancer Survivor Study Cohort, childhood cancer survivors are at significantly higher risk for second neoplasms.[31] A twenty-five year follow-up study of 5760 participants of ALL survivors who were treated between 1970-1986 were compared to the general population and a sibling cohort. They were found to have a higher cumulative mortality of 13% at 25 years from diagnosis, mostly from recurrent ALL and secondary neoplasms.[32] If the pediatric ALL survivor had undergone radiation therapy, or was younger than 5 years old during treatment or experienced a relapse of leukemia, they were at increased risk for adverse long-term outcomes.[32,33] Patients who were in the high risk group undergoing cyclophosphamide chemotherapy may be at an increased risk for acute myeloid leukemia, hepatic dysfunction and bladder cancer as well.[5]

Pain is also an important consideration when treating pediatric cancer survivors. Research conducted by Lu et al. analyzing the results from the Childhood Cancer Survivor Study showed that pediatric cancer survivors experienced more pain than their cancer-free sibling counterparts.[34] Regular acupuncture sessions may be useful for pediatric ALL survivors experiencing pain as a long term sequelae.[35] Female patients were also found to be at an increased risk of pain among pediatric cancer survivors.[34] Another risk factor of having long term post-treatment pain may be having experienced chemotherapy induced peripheral neuropathy (CIPN), which is common in childhood ALL survivors who received vincristine, paclitaxel or cisplatin chemotherapy.[35,36,45] A number of therapies have been researched for CIPN; however, more research is required for this specific patient subset.[45]

Psychosocial treatment, such as counselling, also plays a very important role as there are many mental/emotional aspects of receiving cancer treatment as a child or teenager, such as anxiety of recurrence and eating disorders.[24] Support for these issues can have a profound influence on recovery.[24] For depression, Cognitive Behavioral Therapy (CBT) is an effective treatment for depression and patients should be referred if deemed necessary.[44] Physical exercise has been shown to attenuate depressive symptoms, interpersonal problems, and negative self-esteem issues as well in pediatric cancer survivors.[19]

Fatigue is also a common side effect of pediatric cancer survivors and referrals for psychological and behavioural interventions as well as following proper screening guidelines should be done as there are many underlying health conditions that could be contributing to it.[5] Nutrition and physical exercise may play a role in the severity of fatigue and overall wellbeing for pediatric cancer survivors and should be properly addressed.[5,20]

There have been significant advances in research for naturopathic supportive options for adult survivors of pediatric ALL. However, more research is required on supportive therapies and recommendations that may reduce long-term side effects as a result of treatment.

As part of the patient's healthcare team, naturopathic doctors supporting adult survivors of ALL should establish early and regular communication with the patient's oncologists, family doctors, nurses and/or pharmacists in order to inform them of all of the naturopathic treatments they are receiving in order to ensure safety and efficacy. This collaborative effort among all members of the patient's healthcare team provides optimal patient-centered and focused care.

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