Cover page:

Official Title of the study:

Effectiveness of integrative medicine treatments in lymphoma survivors

Date: July 10th, 2023

Research Plan:

Background:

Lymphoma is the fifth more prevalent type of cancer in Israel, with a 5-year prevalence of 58.41 cases per 100.000 for Non Hodgkin Lymphoma according to the 2020 World Health Organization statistics.[1] Due to scientific progress with novel therapies and better supportive care in the last decades, lymphoma overall survival has increased.[2]

Unfortunately, lymphoma "survivors" whose disease is cured frequently experience physical and psychological long-term effects of the disease and its treatment. For example, psychologic effects and even post-traumatic stress disorder-related symptoms have been described among non-Hodgkin lymphoma (NHL) survivors.[3,4] Decreased physical and cognitive functioning seems to be associated with negative life changes such as impaired financial situation in NHL survivors.[5] Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent symptom in lymphoma survivors, even years after treatment, and is associated with impaired quality-of-life (QoL).[6] Finally, three follow-up studies of the German Hodgkin Study Group have found cancer-related fatigue as a major and debilitating symptom experienced by Hodgkin lymphoma survivors, independently of the type of treatment they received.[7–9] As for CIPN, this symptom was related to impaired QoL,[9] cognitive impairment[10] and decreased social reintegration (return to work, education).[7] While the American Society of Clinical Oncology stated the need of "achieving high-quality survivorship care"[11] and the National Comprehensive Cancer Network (NCCN) established standardized and evidence-based guidelines for the care of cancer survivors,[12] these late effects are still an unmet need.

Integrative oncology (IO) is a "patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments, and aims to optimize health, QoL, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment."[13] It seems that lymphoma survivors use the cited modalities at a rate higher than the general population,[14] with high satisfaction.[15] Indeed, a survey has shown that 61% of NHL survivors use IO, and that such use was associated with a higher perception of cancer-related control (as measured by the 4-question-Perceived Personal Control Scale), and more positive mental functioning.[16] Most of the IO modalities have been tested in cancer survivors, mostly in breast and lung cancers, and have been shown to be safe and effective.[17] For

example, acupuncture alone or combined with other IO modalities, has been shown to improve CIPN severity, including in lymphoma patients.[18] Moreover, cancer-related fatigue may be alleviated by acupuncture, touch therapy, nutritional supplements or homeopathy.[19] Other symptoms such as pain, hot flashes and depression, have been shown to improve by the use of acupuncture among breast cancer survivors, with no serious adverse events.[20] More generally, a review of the use of different integrative modalities has shown that physical activity, diet, dietary supplements, mind-body, acupuncture and touch therapies may improve both physical and emotional issues in cancer survivors.[21] More importantly, these techniques have been shown to improve patient empowerment and enable them to help themselves in an active way.[22] Finally, primary data have shown that IO may even be associated with prolongation of life in cancer survivors.[23] However, in the haemato-oncology setting, the main data on the efficacy of such treatments is during lymphoma, leukemia and myeloma therapy, while much less is known about the approach to lymphoma survivors.[24]

Study aims:

In the present study, we aimed to evaluate if an IO approach may improve QoL, symptoms, financial and social aspects as well as the disease course of lymphoma survivors.

Study plan:

Study setting: We are planning a preference-based comparative effectiveness clinical trial. We will assess whether an IO approach is more effective than a conventional-only approach in the follow-up of lymphoma survivors.

Ethics review: The study protocol was reviewed and approved by the Institutional Review Board in accordance with the Helsinki Declaration (0050-23-BNZ).

Study population: Eligible participants will be recruited from the hematological unit at Bnai-Zion Medical Center in Haifa, Israel. Inclusion criteria: (1) Patients diagnosed with a lymphoproliferative disease, (2) Aged 18 years or older, (3) Received chemotherapy, biological treatment or both for treating the lymphoproliferative disease, (4) Defined in remission for less than one year by the haemato-oncologist (maintenance therapy is authorized), (5) Can respond to questionnaires, and (6) Signed informed consent. There are no exclusion criteria.

Group assignment: Patients will choose to participate in one of two study groups. Patients not willing to come regularly to the clinic for IO treatments will be assigned to the control arm and receive conventional follow-up only according to NCCN guidelines for cancer survivors.[12] Patients willing to attend the IO clinic will be recruited to the intervention arm.

Blinding: Due to the preference assignation, the study will not be blinded.

Intervention: All patients will be followed up by a haemato-oncologist. The frequency and type of visits and exams will be determined by NCCN guidelines,[12] patients' symptoms and physician's clinical judgement. Patients recruited to the intervention arm will receive, on top of the defined conventional medicine follow-up, IO intervention including emotional treatments (counseling, spiritual guidance), complementary medicine (acupuncture, herbal supplements, mind-body, touch and/or movement therapies) or both. The type and frequency of these interventions will be defined by the integrative team in coordination with the patient, based on evidence-based data, patient's symptoms, and preferences. The duration of the intervention will be 6 months from recruitment.

Training and quality control: Complementary medicine practitioners (acupuncturists, naturopaths, mind-body, touch and movement therapists), social workers, dietitians and spiritual guiders who will administer the intervention have at least 5 years of clinical experience in their discipline among patients with oncological or haemato-oncological conditions. A Data Safety Monitoring Board constituted of five experts will control the safety, and quality of the intervention as well as data collection on a yearly basis. Dropout, withdrawal, treatment adherence and uncollected data will be recorded until completion of the study.

Outcomes: The primary outcome will be the effectiveness of an IO approach on improving QoL of lymphoma survivors. The QoL will be evaluated by the EQ-5D questionnaire[25] monthly during the intervention period, and at 3-month post end-of-intervention. This questionnaire has been chosen since it is easy to use, validated, translated into Hebrew, Russian and Arabic, not disease-specific and permits calculation of utility scores and quality-adjusted life years (QALY) allowing economic analysis.[25]

The effect of the intervention on different symptoms experienced by lymphoma patients will be evaluated as a secondary outcome by the Measure Yourself Concerns and Wellbeing (MYCAW) questionnaire that will be filled-out after each intervention, or monthly in the control group and at 3-month post end-of-intervention. The MYCAW questionnaire is appropriate due to its validity, translation into relevant languages, combination of both quantitative and qualitative data, and appropriateness to integrative medicine studies.[26]

Another secondary outcome will be the effect of the intervention on cognitive functions as evaluated once in 3 months by the validated FACT-cog questionnaire[27] and at 3-month post end-of-intervention. Indeed, as previously noted, impaired cognitive functioning is current among lymphoma survivors and has been associated with negative life changes such as impaired financial situation.[5]

The perception of disease control will be evaluated as well as a secondary outcome by filling-out the 4-questions-Perceived Personal Control (PPC) scale[16] once a month in both arms and at 3-month post end-of-intervention, as previous studies showed the association of IO use with a better PPC which is related to more positive mental functioning among lymphoma survivors.[16]

Economic evaluation will be based on both QALY, and a 3-monthly questionnaire on the measurement, valuation, and estimation of costs adapted from a validated questionnaire on informal care.[28]

Finally, the impact of the intervention on lymphoma outcomes (relapse, time-to-relapse, progression-free survival and overall survival) will be evaluated once in 3 months from screening and until 2 years post end of intervention (or 2.5 years from screening for control group) and compared between study groups.

The timing of outcomes' evaluation is summarized in Table 1.

Safety and adverse events: A checklist with acupuncture adverse events based on the AcupAE questionnaire[29] will be used to evaluate acupuncture-associated safety events after each treatment. For non-acupuncture complementary medicine therapies, the practitioner will directly question and evaluate the patient after each intervention for possible safety events. Specifically for dietary and herbal supplements, adverse events and interactions will be evaluated at each visit, and the Naranjo and adapted Drug Interaction Probability Scales (DIPS) will be used to assess the causality of such events with the specific dietary supplements.[30] All adverse events will be recorded, monitored and addressed accordingly. Specific IO interventions may be stopped if significant side effects are of concern. Severe adverse events requiring IO treatment cessation will include anaphylactic shock, pneumothorax, massive bleeding or infection in the acupoint area requiring systemic antibiotic treatment.

Criteria for discontinuation: Participants may be discontinued from the study if they voluntary withdraw informed consent, for safety reasons or due to significant non-compliance with the study protocol as judged by the Principal Investigator. Reasons for discontinuation will be recorded and patients withdrawn from the study will be included in the intention-to-treat analysis.

Sample size calculation: Since no previous study has evaluated similar data, we aimed to obtain a medium effect size (Cohen's d 0.6). Considering a Type I error (alpha) of 0.05, a power of 0.80, and a two-tails comparison of means between the two study groups using

G*Power 3.1.9.4 software, we estimated that to achieve a Cohen's d of 0.6, a minimum of 90 patients (45 patients in each group) was required.

Statistical methods: Data analysis will be performed using IBM SPSS Statistics software. Demographic and clinical data will be analyzed at baseline to measure the balance among the study groups. Quantitative variables will be described using mean and standard deviation or median with range (minimum and maximum) depending on their distribution. Qualitative variables will be described using frequency and percentage distributions. For comparing normally distributed variables between our study groups, we will use the t-test for independent samples. For comparing variables that do not distribute normally between our study groups, we will use the Mann-Whitney test. For comparing qualitative variables between our study groups, we will use the independent Chi-square test and Fisher exact test. Survival analyses will be performed using the Kaplan-Meier product limit survival estimator with log-rank between-group comparison, and Cox regression will be performed for multivariate adjustment of potential confounders. Hazard ratio (HR) with confidence intervals (CI) will be calculated for each independent variable and controlled for all other independent variables in the regression. All comparisons will be two-sided with significance level set at $p<0.05$.

Table 1: Timing of outcomes' evaluation

Timing (months from screening)	0	0-6	1, 2, 4, 5	3, 6, 9	12, 15, 18, 21, 24, 27, 30
MYCAW	X	After each IO session	X	X	
AcupAE / direct questioning for side effects		After each IO session			
EQ-5D	X		X	X	
FACT-cog	X			X	
PPC	X		X	X	
Economic questionnaire	X			X	
Disease assessment	X			X	X

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