Cover page:

Official Title of the study:

Naturopathic-pharmacological consultation on the use of dietary supplements in patients with hematological diseases

Date: August 30th, 2023

BACKGOUND:

Dietary and herbal supplements (DHS) are used by over 50% of the general population and about 30% of patients with hematological diseases (1,2). DHS use involves safety issues related to lack of knowledge and regulation, as well as the risk of side effects and interactions with other DHS and drugs. Indeed, the prevalence of adverse events related to the use of DHS has been estimated at about 20% of DHS users (3-5). These are particularly relevant in patients receiving anticoagulants, chemotherapy, or biological drugs (6-8). On the other hand, DHS may improve various symptoms related to the disease or its treatment (2). For the above reasons, clear and evidence-based guidelines are required for the effective and safe use of DHS in patients with hematological conditions. At Bnai Zion Medical Center, a naturopathic-pharmacological clinical consultation service regarding the use of DHS has been installed in the hematological unit since 2018. The current study aims to examine the effect of such a clinical naturopathic-pharmacological counseling on the effectiveness and safety of the use of DHS in patients with hematological conditions.

METHODS:

Study setting: This is a cross-sectional study that will take place at the Hematology Unit of Bnai Zion Medical Center in Haifa, Israel.

Ethics review: The study protocol was reviewed and approved by the Institutional Review Board in accordance with the Helsinki Declaration (0149-20-BNZ).

Study population: Patients will be referred by the medical or nursing staff of the Hematology Unit at the Bnai Zion Medical Center according to inclusion criteria: (1) Followed up for a hematological condition; (2) Ability to fill simple questionnaires in Hebrew, Russian or Arabic; (3) Indication for consultation: (a) Patient's request to expand knowledge about the use of DHS, (b) Patient using DHS, (c) Patient's desire to start using DHS, (d) Patient that is interested in hearing about the use of DHS for his/her health condition, (e) Medical or nursing team's recommendation to take DHS for medical treatment or to improve compliance with conventional treatment. There are no exclusion criteria. After explanation and agreement to participate in the study, the patient will be asked to sign an informed consent form.

Intervention: The naturopathic-pharmacological consultation includes a naturopath and a clinical pharmacist and will be recorded in the computerized system with a copy given to the patient, the attending hematologist, the naturopath, and the clinical pharmacist. It will consist of at least two meetings:

First meeting: The patients will be asked to document the DHS that they use or intend to use, or the extent and interests they have in this regard. Socio-demographic and medical data will be recorded based on anamnesis and a look at the patient's chart, with an emphasis on regular medications (anticoagulants, chemotherapy) and compliance with treatment, and relevant laboratory results (blood count, coagulation) if necessary. A safety assessment will be performed based on the above data, by the clinical pharmacist, and with the help of scientific databases. An effectiveness assessment will be carried out by the naturopath and with the help of scientific databases. The meeting will conclude with a recommendation to start, stop, or continue treatment with certain DHS, and will be recorded in the computer system.

Follow-up meetings: The second meeting will be held physically or digitally at least a week after the first meeting, and additional meetings will be held as needed, on the recommendation of the medical or nursing staff, the patient himself, the naturopath, or the clinical pharmacist. At these meetings, the safety and effectiveness of the supplements will be evaluated based on the patient's questionnaire and the effect on compliance with treatment with conventional drugs.

Training and quality control: The naturopaths who will be involved in the consultation have at least 5 years of clinical experience among patients with oncological or haemato-oncological conditions. The clinical pharmacist involved in the study has a third degree (PhD) in clinical pharmacy and specialized on dietary and herbal supplements. 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:

Primary outcome: The primary outcome will be the safety of the use of DHS in patients with a hematological disease through naturopathic counseling. This will be documented by the number of potential interactions with moderate to major level of significance prevented by such consultation in each patient, as well as the incidence of

DHS-related safety events. The Naranjo and modified FDA algorithm will be used to assess the causality of such events with the specific dietary supplements (9), and only side effects at least possibly caused by the DHS according to these scales will be considered.

Secondary outcomes:

The efficacy of the different prescribed DHS will be assessed by symptom relief as measured by the Measure Yourself Concerns and Wellbeing (MYCAW) questionnaire that will be filled at the first meeting before the consultation, and again at each meeting. 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.

Patient-physician communication around the use of DHS will be described before, during and after the series of consultations by asking the patient whether the topic has been brought up with the treating hematologist and checking the documentation of the use of DHS in the medical charts.

Satisfaction of the patients will be evaluated by a direct question asked after each meeting ranking in a 1-5 Likert scale the satisfaction of the patient from the consultation.

Compliance with hematological treatment will be calculated by the relative dose intensity (RDI) of the prescribed hematological drugs both before and after intervention.

Finally, a qualitative evaluation of the staff and patients from naturopathic-pharmacological counseling will be assessed. Indeed, semi-structured in-depth interviews will be conducted with patients who are interested in participating in the qualitative arm (10-15 patients) and the staff members involved (medical staff, nursing staff, naturopath, clinical pharmacist). The goal is to describe the process of building the naturopathic-pharmacological consultation and evaluate the satisfaction of the staff and patients in a qualitative manner, in order to complete the quantitative assessment that will be carried out in the consultation itself.

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 the prevalence of DHS-related side effects has been estimated at 18% of DHS users in a previous study (5) and that DHS-drug interactions may cause about half of such side effects, we estimated that the prevalence of DHS-related adverse events in patients undergoing naturopathic consultation will be about 10%. Based on these data, we calculated the minimal sample size with Scalex and ScalaR calculators (10). With a level of confidence of 95% (alpha 5%), a precision of 10% and an estimated prevalence of 10% of adverse events, we needed a minimum of 35 patients in the study.

Statistical methods: Data analysis will be performed using IBM SPSS Statistics software. Demographic and clinical data will be analyzed at baseline. 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 recruitment and post-intervention, we will use the paired t-test. For comparing variables that do not distribute normally between the different time points, we will use the Mann-Whitney test. For comparing qualitative variables between time points, we will use the independent Chi-square test and Fisher exact test. All comparisons will be two-sided with significance level set at $p<0.05$.

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