Cover page:

Official Title of the study:

Effectiveness and safety integrative therapies in multiple myeloma

Date: July 15th, 2024

Research Plan:

Background:

Multiple myeloma (MM) is a hematologic malignancy that can cause anemia, renal failure, bone disease, and hypercalcemia [1]. Today MM is considered a chronic disease and most patients will receive ongoing biological treatments. As a result, this disease causes a number of symptoms related to the disease itself or its treatment, which include, among others, weakness and fatigue, bone or nerve pain, depression and anxiety, gastrointestinal symptoms, impairment of sexual function, etc. These symptoms cause significant damage to quality-of-life (QoL) [2] which is similar in patients who receive different treatment lines [3]. As a result, the FDA emphasized QoL as a key outcome for the approval of new drugs for the disease [4].

The conventional therapeutic approach to the various symptoms is based on supportive care guidelines including pharmacological and non-pharmacological treatment of pain, gastrointestinal symptoms, psychological components, etc [5]. These treatments involve side effects and usually refer to individual symptoms.

Complementary and integrative medicine includes treatments of touch, movement, mind-body, acupuncture, nutrition and nutritional supplements. Many studies have shown the effectiveness of these treatments on various symptoms in cancer patients including pain, depression and anxiety, fatigue and weakness, gastrointestinal symptoms, etc [6-8]. In MM patients, the effect of diet and nutritional supplements was mainly examined, but there is also little information on the effectiveness of mind-body treatments on symptoms of anxiety and depression, as well as acupuncture on neuropathy or on symptoms experienced by MM patients around autologous bone marrow transplantation [9].

In recent years, a wide variety of new drugs have entered the market that cause side effects that were unknown until now and little is known about the effect of complementary medicine treatments on symptoms and QoL of MM patients since the development of these drugs.

In this study we will examine the effect of complementary and integrative medicine treatments (including acupuncture, touch, movement, mind-body) on the QoL and symptoms that characterize MM patients during treatment with different lines of therapy, including new drugs.

Study aims:

In the present study, we aimed to evaluate if integrative therapies may improve QoL, symptoms, financial and social aspects as well as the disease course of MM patients.

Study plan:

Study setting: We are planning a preference-based comparative effectiveness clinical trial. We will assess whether integrative medicine is more effective than a conventional-only approach for improvement of QoL in patients with MM.

Ethics review: The study protocol was reviewed and approved by the Institutional Review Board in accordance with the Helsinki Declaration (0054-24-BNZ).

Study population: Eligible participants will be recruited from the hematological unit at Bnai-Zion Medical Center in Haifa, Israel. Inclusion criteria: (1) Age over 18, (2) Diagnosis of multiple myeloma, (3) Possibility to answer questionnaires once a month in Hebrew, Arabic or Russian, (4) Signing an informed consent form. Exclusion criteria include (1) Age under 18 years, (2) In patients who will receive acupuncture: platelet level below 20x10^9/L, (3) In patients who will receive reflexology: deep vein thrombosis in the leg, (4) Hemodynamic instability, (5) Psychiatric disorder impairing competence.

Group assignment: Patients will choose to participate in one of two study groups. Patients willing to attend weekly integrative medicine treatments will be recruited to the intervention arm. Patients not willing to come regularly to the clinic for integrative medicine treatments will be assigned to the control arm and receive conventional therapy only.

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

Intervention: All patients will receive conventional MM treatment at the hemato-oncology department. Patients recruited to the intervention arm will receive, on top of the defined conventional treatment, integrative medicine intervention including acupuncture, touch and/or mind-body therapies. 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 intervention will be given once weekly for 6 weeks. Patients in the intervention arm and patients in the control arm that are willing to do so will fill questionnaires as of study protocol. The investigators will collect socio-demographic and medical data from medical charts of patients from both study arms.

Training and quality control: Complementary medicine practitioners (acupuncturists, touch and mind-body therapists), 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 integrative medicine on improving QoL of MM patients. The QoL will be evaluated by the EORTC QLQ-MY2 (European Organization for the Research and Treatment of Cancer Quality of Life for Myeloma patients) score at 1-2 weeks after end-of-treatment in intervention group and 7-8 weeks after recruitment in control group. It comprises 20 questions that address four myeloma-specific Heath-related QoL (HRQoL) domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Domain scores are averaged and transformed linearly to a score ranging from 0-100. A high score for Disease Symptoms and Side Effects of Treatment represents a high level of symptomatology or problems, whereas a high score for Future Perspective and Body Image represents better outcomes [10].

General HRQoL will be evaluated as well as a secondary outcome using the European Organization Research for Treatment of cancer core quality of life (EORTC-QLQ-C30) questionnaire summary score at 1-2 weeks after end-of-treatment in intervention group and 7-8 weeks after recruitment in control group. It is calculated from the mean of 13 of the 15 quality-of-life (QLQ-C30) scales of the questionnaire = (Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ 100-Fatigue+ 100-Pain+ 100-Nausea_Vomiting+ 100-Dyspnoea+ 100-Sleeping Disturbances+ 100-Appetite Loss+ 100-Constipation+ 100-Diarrhoea)/13. Scores range from minimum 0 to maximum 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms [10].

The effect of the intervention on different symptoms experienced by MM patients will be evaluated as a secondary outcome by the Edmonton Symptom Assessment System (ESAS) at 1-2 weeks after end-of-treatment in intervention group and 7-8 weeks after recruitment in control group. It assesses the severity over time of nine symptoms common among patients with cancer and other advanced illness: pain, tiredness, drowsiness, nausea, shortness of breath,

appetite, depression, anxiety, and wellbeing. A higher score represents a higher ("worse") level of symptoms [11].

Compliance to conventional MM treatment will be assessed by calculating the Relative dose intensity (RDI) which is the ratio of delivered dose intensity (DDI) of myeloma treatment with standard dose intensity (SDI) of myeloma treatment = DDI/SDI, during the one year following recruitment.

Economic evaluation will be based on the EuroQol-5 Dimension (EQ-5D) questionnaire at 1-2 weeks after end-of-treatment in intervention group and 7-8 weeks after recruitment in control group. 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 [12].

Finally, the impact of the intervention on MM treatment outcomes (overall response rate, progression-free survival and overall survival) will be evaluated once in 3 months from screening and until 2 years post recruitment and compared between study groups.

Safety and adverse events: A checklist with acupuncture adverse events based on the AcupAE questionnaire [13] 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. Specific integrative medicine interventions may be stopped if significant side effects are of concern. Severe adverse events requiring 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 $p<0.05$.

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