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The Effect of Mind-Body Intervention on Lymphocyte Doubling Time and Treatment-Free Survival in Treatment-Naïve Chronic Lymphocytic Leukemia Patients

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Keywords
Cancer · Mind-body · Chronic lymphocytic leukemia · Watch and wait

Abstract

Introduction: Mind-body intervention (MBI) serves as a supportive aid in oncology. We hypothesized that MBI could impact the progression of chronic lymphocytic leukemia (CLL) in the "watch and wait" (w&w) phase. ***Methods:*** We conducted a non-randomized, prospective controlled study between the years 2020 and 2022 on 76 treatment-naïve CLL patients in the w&w phase. Thirty-seven patients were included in the intervention arm and received MBI, while 39 patients were included in the control group. The primary and secondary endpoints were prolongation of lymphocyte doubling time (LDT) and treatment-free survival (TFS). LDT was compared at 0, 180, 360, and 540 days using paired *t* tests. TFS was compared between the intervention and control groups using the log-rank test. Cox proportional hazards models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for TFS in the intervention group compared to the control, stratified by the study covariates. ***Results:*** MBI prolonged LDT at all time points, including at day 360 (median of 2.47 years; CI 1.05–3.9; $p = 0.001$). TFS at 18 months was longer in the intervention group compared to the control group (HR 0.23; CI 0.06–0.79, $p = 0.01$). ***Conclusions:*** MBI was associated with prolonged LDT and TFS in patients with CLL in the w&w phase. These results provide a basis for a larger randomized controlled trial.

Introduction

Depression, stress, and anxiety potentially correlate with malignant diseases and their prognosis [1–8]. Among the mechanisms suggested for this correlation are activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, increasing production and secretion of related hormones and cytokines, such as interleukin (IL)-6 and glucocorticoids [1, 2, 5].

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Abnormalities in the hypothalamic-pituitary-adrenal axis have been demonstrated in cancer patients and linked to resistance to chemotherapy, promotion of angiogenesis via delivery of vascular endothelial growth factor (VEGF), and decreased apoptosis [2]. Possible additional mechanisms include the reduced activity of natural killer (NK) cells [4, 6], altering the balance between type 1 and type 2 T-helper cells (Th1 and Th2) in favor of Th2. Dominance of Th2 leads to higher levels of IL-6, reduced production of NK cells, reduced cytotoxic T-cell activity [6, 9]. Telomere shortening is an additional suggested mechanism [10, 11].

Mind-body intervention (MBI), or mind-body therapy/practice/medicine, was introduced in September 2000 by the United States National Center for Complementary and Integrative Health. MBI gathers therapies, as well as physical and mental rehabilitative practices, which focus on the relationships between the brain, mind, body, and behavior, and their effect on health and disease [9]. The list of activities which are part of MBI includes mindfulness, guided imagery, meditation, yoga, and many more.

MBI was shown to be associated with suppressing proinflammatory cytokines, such as IL-6, and increase of NK cell function and telomerase expression [4, 10]. MBI has been proven to have positive, measurable effects on various benign conditions, such as chronic back pain [12, 13]. In the care of cancer patients, MBI is accepted as a supportive aid to conventional medicine to improve quality of life and compliance with therapeutic regimens [14]. However, the effect of MBI on the course of malignant diseases has rarely been investigated, and the studies which were published show equivocal results. Eckerling et al. [2] reviewed 22 studies investigating the effect of different protocols of MBI and psychosocial interventions on the outcome of several cancer types, all of which were solid tumors that were also treated conventionally. Among them, eight studies demonstrated survival advantage. Nevertheless, the authors concluded that there is no clear evidence for improved long-term outcomes.

For most cancers, therapy is initiated at diagnosis. However, with chronic lymphocytic leukemia (CLL), the standard of care is active surveillance until treatment is needed [15]. About 70% of CLL patients are diagnosed at an asymptomatic, early disease stage and followed for a long w&w period [16]. Fluctuations in lymphocyte count are not uncommon, and rare spontaneous remissions may occur [17].

According to international guidelines, the indications for CLL treatment initiation are hemoglobin <10 g/dL, platelet count <100,000 × 10^6/L, massive splenomegaly, massive lymphadenopathy, rapid lymphocyte doubling time (LDT) of less than 6 months, and disease-related symptoms, such as night sweats and fever [16]. A rapid doubling time is a bad prognostic factor, reflective of a more aggressive course of the disease [18, 19].

Several predictive models are designed to predict the period between diagnosis and treatment initiation [20]. For example, the International Prognostic Score for Early Stage CLL (IPS-E) model is based on three parameters: unmutated immunoglobulin heavy chain variable region gene (IgHV), absolute lymphocyte counts higher than 15,000 × 10^6/L, and presence of palpable lymph nodes at diagnosis [21].

Since there are suggested mechanisms which connect mind and body in cancer, and there is some evidence that supports the effect of MBI on these mechanisms, we hypothesized that MBI might affect objective parameters of CLL, rather than utilized as supportive aid only. Due to the indolent nature of CLL and the w&w phase, without any pharmacological treatment, we chose this condition in order to investigate the effect of MBI on the course of cancer.

Materials and Methods

Study Design

Preliminary Pilot Study

We conducted a small pilot study on treatment-naïve patients with CLL during the w&w phase from March 2018 to January 2020 to assess the likelihood of confirming our hypothesis. The insights gained from the pilot study paved the way for a more extensive and controlled trial, which was subsequently undertaken.

Non-Randomized Controlled Prospective Study

A prospective, non-randomized comparative intervention study was conducted over 2 years, from February 2020 to February 2022, in Israel. We chose to focus on CLL patients with progressive disease who do not fulfill the criteria for treatment initiation.

Inclusion criteria were as follows: (1) patients with CLL for at least 1 year, (2) documented LDT <4 years, (3) absolute lymphocyte count>15,000 × 10^6/L, hemoglobin >10 g/dL, and platelet count >100,000 × 10^6/L at enrollment, and (4) no absolute indication for treatment initiation. We excluded patients with a history of concomitant psychiatric disorders other than nonpsychotic depression or anxiety and those with active cancer other than CLL or a life expectancy of less than 1 year. Primary and secondary endpoints were defined as prolongation of LDT and treatment-free survival (TFS), respectively.

Candidates were identified based on data provided by Maccabi Health Services, Israel's second largest Health Maintenance Organization. Patients were offered to participate in the trial. Those not interested in participating in the suggested intervention were asked to serve as a control group. Enrolled participants signed an

informed consent. All patients were routinely followed up by their treating hematologist, and a complete blood count was performed at least every 3 months. Demographic, clinical, and laboratory parameters were collected from the computerized medical charts. Cytogenetics abnormalities were tested by fluorescence in situ hybridization and were considered a positive result when a clone was identified in >5% of cells. Polymerase chain reaction tested IgHV mutation status. Data regarding the use of antidepressant medications was drawn from the patients' medical files.

Thirty-six hematologists treated the participating patients. The treating hematologist was aware of the study but was not part of the research team and made independent decisions.

The MBI Model

The MBI model used in this study was designed by the principal investigator (S.S.) and is based on the resemblance between processes occurring in one's subconscious and in the biology of cancer. This is a divergent and original approach to cancer intervention. The pathogenesis of cancer is based on a multiple hit hypothesis in which progressive genomic and cellular events result in autonomous and aberrant cell development [22]. The first hit possibly provides an advantage, while the last hit leads to unregulated function which was once of value. Cancers derived from infections, such as mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach, can serve as an example. The first event is the development of an ectopic lymphatic tissue in the stomach to cope with Helicobacter pylori infection, while the last event is nonregulated proliferation of the same tissue [23]. Similar sequence of events, or hits, occurs in the subconscious, which is the major part of the human mind. During the first years of life, children assimilate into their subconscious beliefs and axioms, which generate patterns of behavior that aim to ensure the reception of love and security. Since these beliefs reside in the subconscious, they operate automatically, which is neither adaptive nor flexible. This cascade evolves into inner conflicts and inherent stress [24]. As mentioned above, stress might have a role in cancer initiation and progression, and thus, serve as a bridge between mind and body.

Based on the similarity described above, an intervention model was developed and used in this study. The intervention model comprised of three levels: (i) behavioral and cognitive level, which aims to promote relaxation and parasympathetic activity by using several measures such as mindfulness, (ii) psychological level aiming to unmask core beliefs from the subconscious to promote awareness and thus shift from an automatic to a choice mode, (iii) spiritual level, gained mainly by meditation and guided imagery support processes in levels (i) and (ii). Detailed description of the model can be found under the online supplementary section (for all online suppl. material, see https://doi.org/10.1159/000538055) (CCRC model).

The Intervention Protocol

The intervention included both individual and group meetings. Due to the COVID-19 pandemic, part of the meetings was held online. Individual sessions primarily addressed the psychological aspect, whereas group sessions focused on behavioral and spiritual dimensions, serving as a supportive network for participants. Initially, individual sessions occurred weekly for the first 6 weeks, transitioning to bi-monthly meetings until the conclusion of the first year, and monthly sessions during the second year. Each individual session spanned 1–1.5 h, incorporating activities such as meditation, relaxation, and conversation. Group sessions took place monthly throughout the entire study period, lasting 2 h. These group sessions included discussions on the therapeutic model, conversations, sharing experiences, and meditation, among other activities, with an average of approximately 10 participants per group.

Statistical Analysis

Analyses were performed using Python version 3.1 with the stats model package and PRISM version 8.0.1, San Diego, CA, USA. Descriptive parameters were described as mean and standard deviation. TFS is the time between enrollment and therapy initiation or the patient's death. LDT was calculated at several time points (540 days, 360 days, 180 days before enrollment, at enrollment date, and 180 days, 360 days, and 540 days after enrollment) by applying regression analysis over a minimum number of 3 observations in the year before the time point. The LDT was presented by log (2)/m, where m is the estimate of the slope of the linear regression curve of log values. The time points appointed after pharmacological treatment initiation were excluded. LDT was categorized to be shorter than 1 year (<1), 1–3 years (1–3), and longer than 3 years (>3) for descriptive purposes. The number of days to doubling was divided by 365, with 10 years capped as the upper limit of doubling time. The LDT before and after intervention were compared in the intervention and the control group using the paired t test. Significance was determined at p value <0.05. Using the log-rank test, the Kaplan-Meier curves were plotted to compare TFS between the intervention and the control groups. Cox proportional hazards models were used to calculate the hazards ratios (HRs) and the 95% confidence intervals (CIs) for TFS in the intervention group compared to the control group, stratified by the study covariates.

Results

A Preliminary Pilot Study Showed Prolongation of LDT

The preliminary pilot study included 6 CLL treatment-naïve patients in the w&w phase and was conducted from March 2018 to December 2019. We observed a noteworthy trend in the average LDT of the entire group, which increased from 2.2 years to 4.8 years within 3 months of intervention initiation. Although the statistical significance was not achieved within this small group ($p = 0.1375$, see online suppl. Fig. 1), the observed outcome supported our hypothesis and further investigation. Building upon these encouraging findings, we designed a larger and controlled study.

A Non-Randomized Controlled Interventional Study Was Completed Successfully with Few Study Discontinuations

Seventy-nine treatment-naïve CLL patients were enrolled to the study between February 2020 and February 2021. Forty patients were enrolled in the intervention arm and 39 in the control. Two patients from the intervention

Table 1. Baseline characteristics of the study cohort

Variable	All (n = 76)	Control (n = 39)	Case (n = 37)	p value
Age, mean (SD), years	63.1 (9.0)	64.7 (9.1)	61.4 (8.5)	0.11
Female sex, n (%)	25 (33)	13 (33)	12 (32)	0.87
Time since diagnosis, mean (SD), years	5.5 (4.0)	6.0 (4.4)	4.9 (3.4)	0.23
Blood count				
Lymphocyte count, mean, k/mL (SD)	57,148 (35,489)	58,277 (33,670)	55,958 (37,273)	0.78
Hemoglobin, mean, g/dL (SD)	13.5 (1.5)	13.4 (1.7)	13.6 (1.3)	0.47
Platelets, mean, k/mL (SD)	182.8 (48.8)	174.4 (43.4)	191.6 (52.5)	0.13
IgHV mutation status (mutated, unmutated)	(30, 15)	(11, 6)	(19, 9)	0.83
Cytogenetic abnormalities				
17p-/p53 (yes, no)	(9, 16)	(5, 11)	(4, 5)	0.82
11q- (yes, no)	(6, 17)	(2, 12)	(4, 5)	0.26
13q- (yes, no)	(22, 9)	(13, 4)	(9, 5)	0.73
Trisomy 12 (yes, no)	(6, 16)	(4, 9)	(2, 7)	0.96
RAI stage				0.99
0	27	15	12	
1	28	15	13	
2	17	9	8	
N/A	4	3	1	
IPS-E				0.42
Low risk – 0	16	5	11	
Intermediate risk – 1	17	6	11	
High risk – 2, 3	15	8	7	
N/A	28	20	8	
Lymphadenopathy at diagnosis (yes, no)	(19, 53)	(9, 27)	(10, 26)	1.0
Lymphocyte count ≥15,000 at diagnosis (yes/no), n (%)	26/75 (35)	16/38 (42)	10/37 (27)	0.23
LDT at enrollment				0.13
Less than 1 year	14	8	6	
1–3 years	33	13	20	
More than 3 years	16	11	5	
N/A	13	7	6	
SSRI (yes, no)	(14, 62)	(8, 31)	(6, 31)	0.85

Patients' characteristics at study enrollment. IGHV, immune globulin heavy chain variable; SSRI, serotonin selective reuptake inhibitor (antidepressant); IPS-E, international prognosis score for asymptomatic early stage chronic lymphocytic leukemia; LDT, lymphocyte doubling time; SD, standard deviation.

group withdrew their participation within 1 month, and an additional patient was diagnosed with metastatic squamous cell carcinoma (SCC) immediately after enrollment and started immune chemotherapy. These 3 patients were excluded; the final analysis included 37 patients in the intervention arm. One patient was diagnosed with squamous cell carcinoma 1 year after enrollment and required chemo-immune therapy during the intervention period. Two additional patients decided to withdraw their participation after 8 months of intervention. One patient in the control group was diagnosed with lung cancer 4 months after enrollment and died shortly after without treatment. These 4 patients were included in the final analysis.

Patients Included in Both Study Groups Exhibit Similar Demographic and Clinical Features

The characteristics of the study participants by study group are depicted in Table 1. Patients in both groups were similar in age and sex. Clinical parameters were similar as well – time from diagnosis to study enrollment, lymphocyte count, hemoglobin level, and platelet count at enrollment.

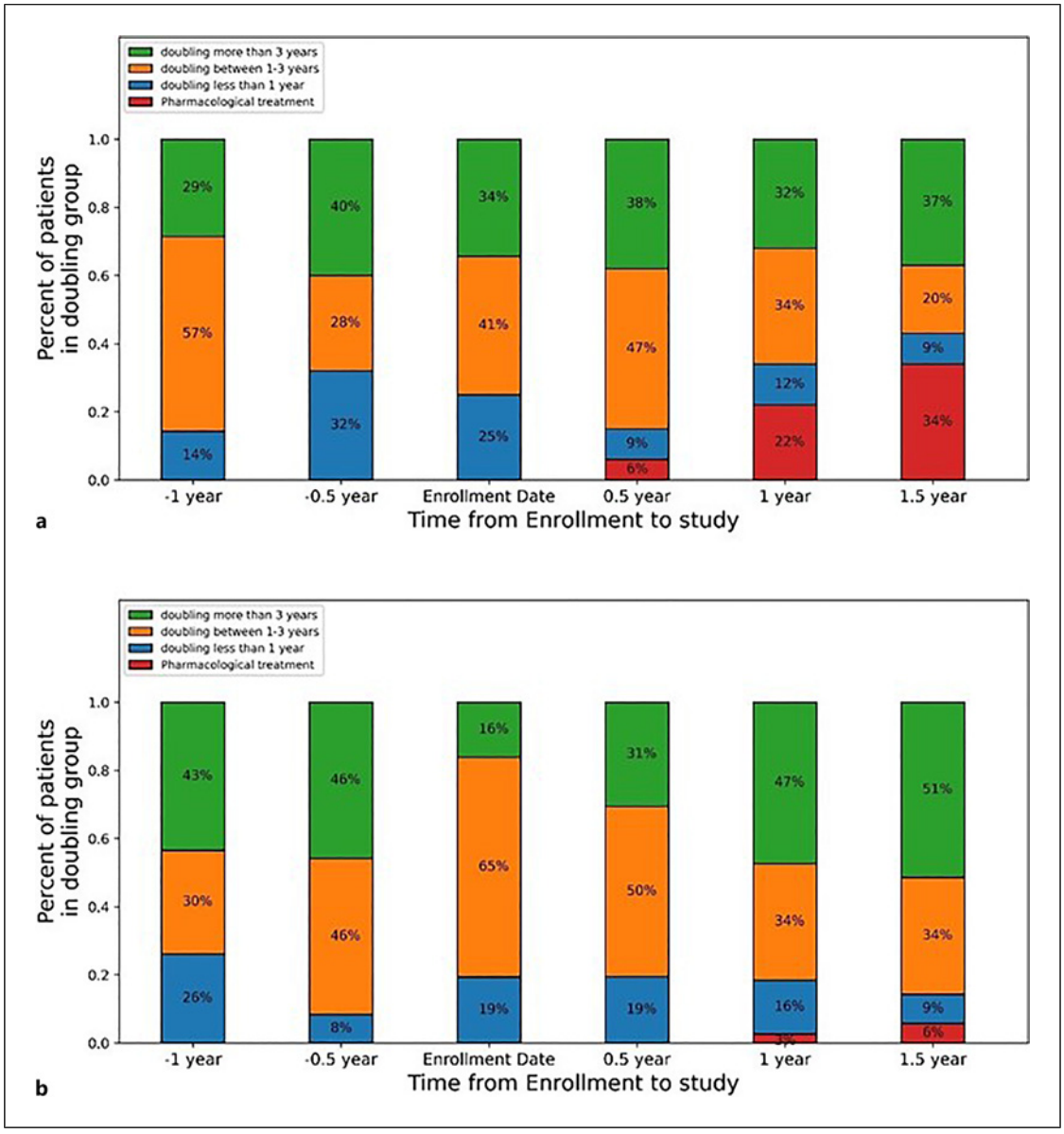

Fig. 1. Mind-body intervention (MBI) prolongs LDT and TFS in treatment-naïve chronic lymphocytic leukemia patients (CLL). Doubling time and pharmacologic treatment categories frequencies of the control arm (**a**) and the intervention arm (**b**) in different time points of the study, before and after enrollment.

IgHV mutation status was tested in 46/76 patients (60%). Mutated IgHV was identified in 31/46 (67%) patients, of which 12/18 (66%) in the control arm and 19/28 (68%) in the intervention arm. Cytogenetics abnormalities were not different between groups. A low to intermediate IPS-E score (0–1) was identified in 22/29 (75%) patients in the intervention arm and 11/19 (57%) in the control arm ($p = 0.42$). RAI stage at enrollment was documented in 72/76 (94%) and was not different between the groups ($p = 0.99$). The use of antidepressants, all of which were selective serotonin reuptake inhibitors (SSRI), was similar between the intervention group (16%) and the control group (20%, $p = 0.85$).

Descriptive Analysis Suggests Better Outcome in the Intervention Group

Figure 1 illustrates both study groups' LDT categories and pharmacological treatment over time. At enrollment, both groups were generally similar. Half a year from enrollment, 6% of controls started pharmacological

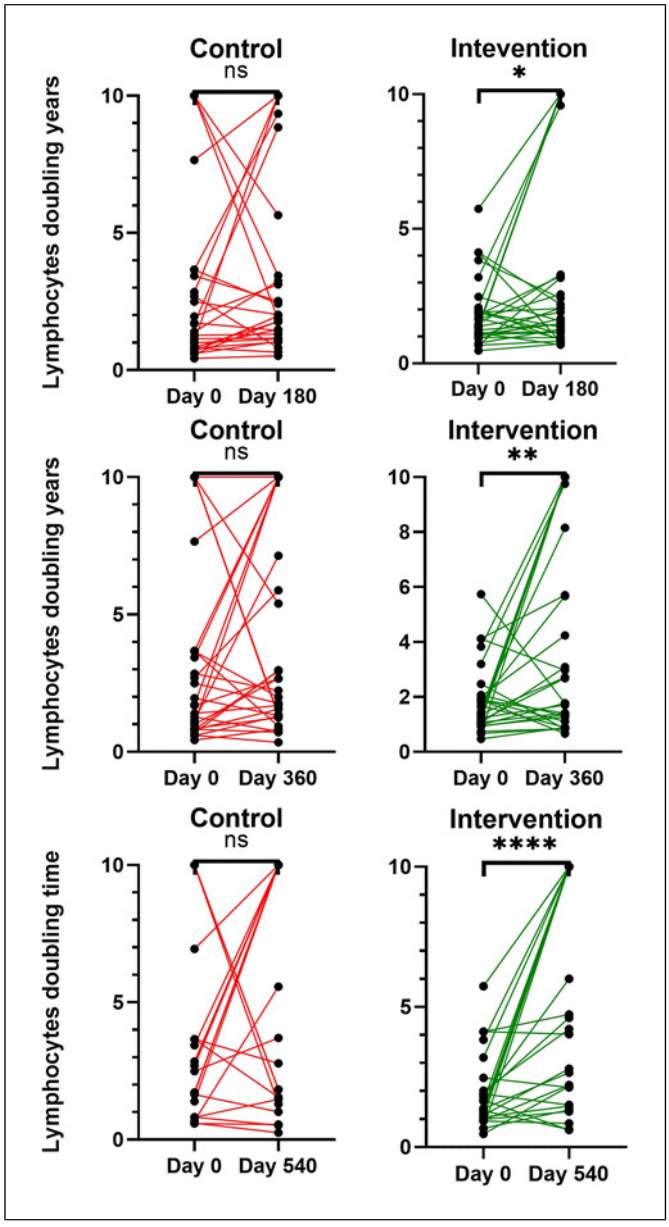

Fig. 2. Prolongation of lymphocyte doubling time (LDT) in the intervention arm but not in the control arm. Doubling time in years of patients in the control arm (left) and the intervention arm (right), the statistical significance was calculated using the paired *t* test; *p = 0.02; **p = 0.001; ****p = 0.0001.

treatment; the proportion of LDT >3 years in the control group remained practically unaltered. Concomitantly, the proportion of the intervention group with LDT >3 years almost doubled to 31%. Moreover, 1 year after enrollment, the proportion of controls who started pharmacological treatment increased to 22%. During the same time, 3% of treated patients started pharmacological treatment, and those with LDT >3 years increased to 47%. A year and a half after enrollment, these trends further increased: 34% of controls were under pharmacological treatment, and 37% had LDT >3 years. Comparatively, only 6% of the treatment group were under pharmacological treatment, and 51% had LDT >3 years.

LDT Was Consistently Prolonged in the Intervention Group Compared to the Control Group

Comparing the within-patient LDT by time from enrollment (Fig. 2), there were significant increases in the intervention group at 180 days (mean difference (MD) 1.42 years; 95% CI 0.23–2.26; p = 0.02), 360 days (MD 2.47 years; CI 1.05–3.9; p = 0.001), and 540 days (MD 3.24 years; CI 1.76–4.76; p = 0.0001). During these time intervals, there were no significant changes in LDT in the control group at 180 days (MD 0.57 years; 95% CI −0.89 to 2.03; p = 0.43), 360 days (MD 0.79 years; CI −0.82 to 2.4; p = 0.32), and 540 days (MD 1.4 years; CI −1.32 to 4.12; p = 0.29).

TFS Was Prolonged in the Intervention Group Compared to the Control Group with Greater Effects in Some Subgroups

Figure 3 presents the TFS analyses of the control and intervention groups. Three patients (6%) from the intervention group and twelve (34%) from the control group had started pharmacological treatment for CLL. One patient from the control group has died from lung cancer. TFS was significantly longer in the intervention group (log-rank test p = 0.01), yielding an HR of 0.23 (95% CI 0.06–0.79).

When including the 3 patients enrolled in the study who were excluded from the intervention arm shortly after their enrollment, one initiated pharmacologic treatment for CLL after 2 months, and one died from metastatic SCC 8 months later. In an intention-to-treat analysis using log-rank analysis, the TFS prolongation in the intervention group was still statistically significant with p = 0.04 (online suppl. Fig. 2).

Figure 4 presents the HR for TFS stratified by study covariates. Milder disease, as reflected by low IPS-E score and low RAI stage at enrollment (HR 0.09; CI 0.01–0.73, p = 0.02), initiation of MBI within 5 years from CLL diagnosis (HR 0.09; CI 0.01–0.71, p = 0.02), and male gender (HR 0.11; CI 0.01–0.89, p = 0.04) were predictive of better TFS with MBI. Patients who were treated with SSRI had less benefit from MBI. However, IgHV mutation status and cytogenetics abnormalities did not impact the effect of MBI. Results were unchanged when adjusted to age and sex (online suppl. Fig. 3).

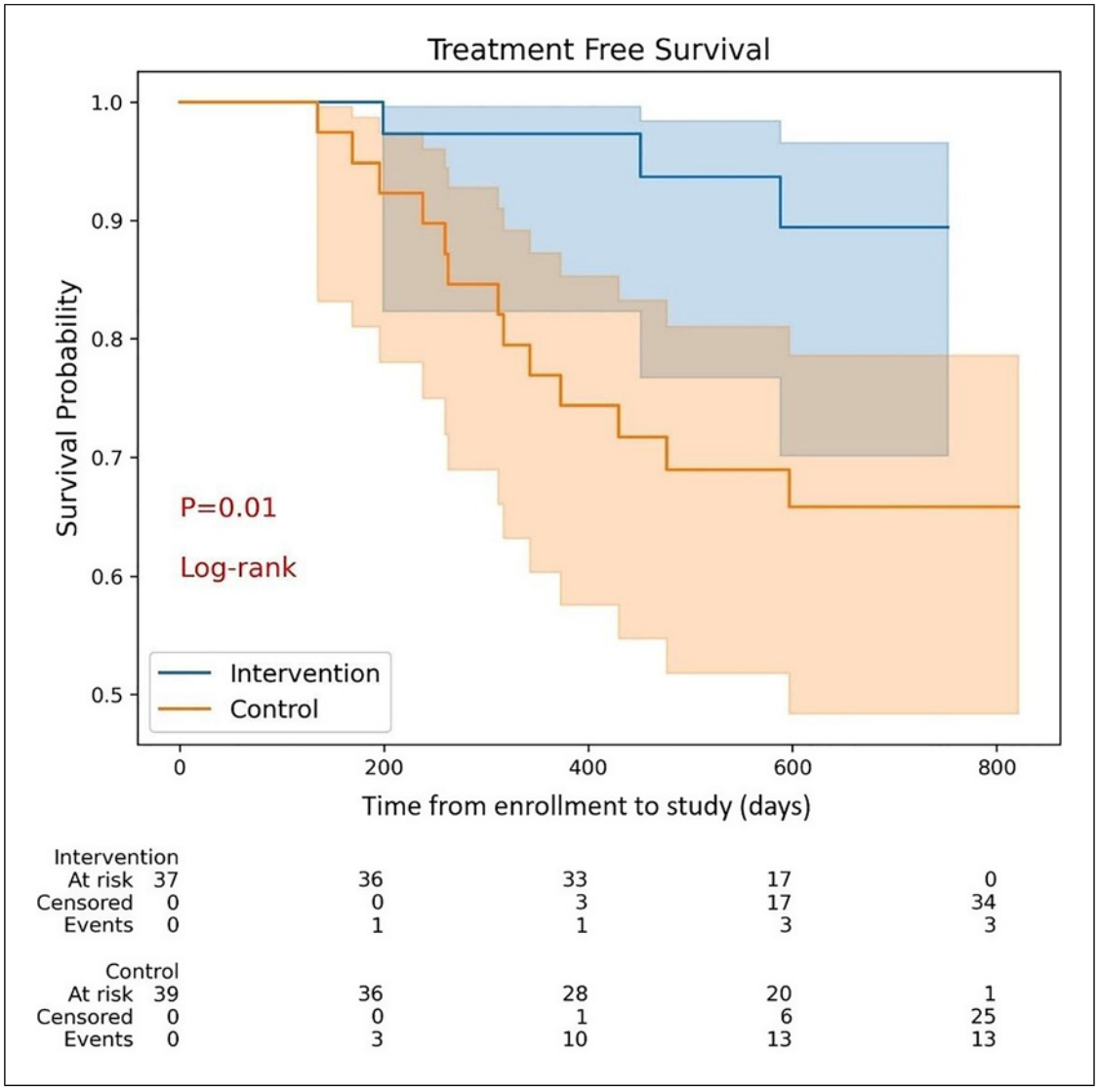

Fig. 3. Mind-body intervention (MBI) prolongs TFS time in treatment-naïve chronic lymphocytic leukemia patients (CLL). Kaplan-Meier curve for patients in the intervention arm (blue) and the control arm (orange). The number at risk is presented for each group. Statistics were calculated with the log-rank (Mantel-Cox) test. 0 = 0.01.

Discussion

In this study, we observed that CLL-naïve patients in the watch and wait (w&w) phase who underwent MBI demonstrated a longer LDT and improved TFS compared to the control group without any pharmacological treatment. CLL was chosen for this purpose due to its unique w&w phase, allowing for a pure MBI approach without confounders of conventional pharmacologic, radiation, or surgical treatments. The indolent course of CLL provided a long period of w&w, facilitating the implementation of MBI. Additionally, CLL is clinically easy to follow, with physical examination and basic blood tests.

Key characteristics of CLL are defects in the immune system and the ability of leukemic cells to evade immune defenses and induce immunosuppression, resulting in disease progression. This is partially attributed to impaired NK activity [25] and increased levels of IL-6 [26]. Thus, we hypothesize that the beneficial effects on prolongation of LDT and TFS may be associated with a decrease of IL-6 levels, increase of NK cells activity, and a possible shift in the

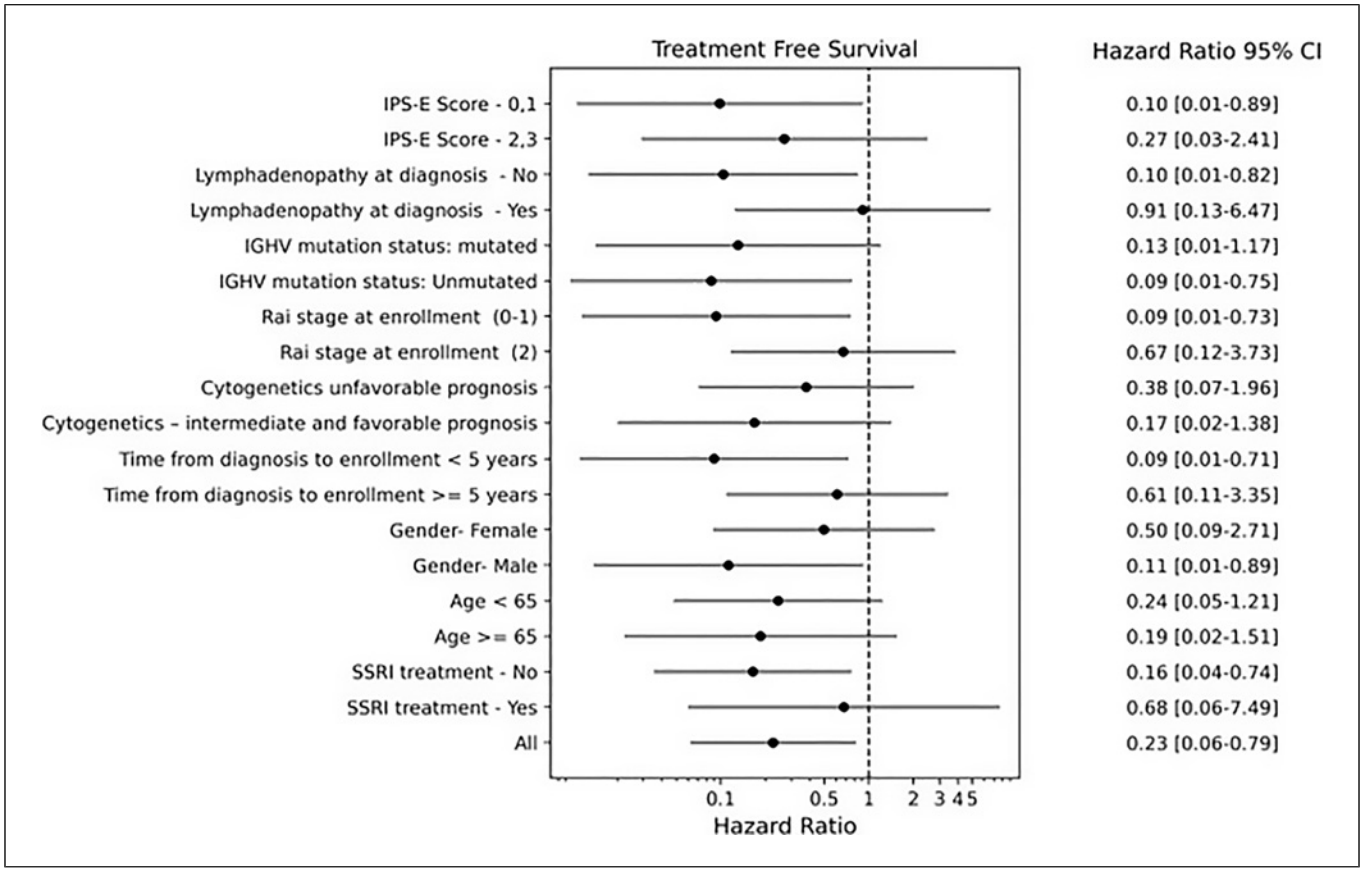

Fig. 4. Patient's baseline characteristics predict treatment-free survival (TFS) in treatment-naïve chronic lymphocytic leukemia patients (CLL) receiving mind-body intervention (MBI). Forest plot presenting the HR and 95% CI of TFS in patients in the intervention arm compared to the control arm. Statistics were calculated using the cox regression and log-rank (Mantel-Cox) test. IGHV, immune globulin heavy chain variable; SSRI, serotonin selective reuptake inhibitor (antidepressant); IPS-E, international prognostic score for asymptomatic early stage chronic lymphocytic leukemia; LDT, lymphocyte doubling time.

Th1 versus Th2 balance, to create an anticancer effect. We intend to test these hypotheses in follow-up studies, in order to define the mechanism of action of MBI.

Prolongation of LDT was also evident in the control arm of the study. This occurrence is likely attributable to the commencement of pharmacological treatment in 34% of the patients, who were deducted from the group out over time. In contrast, within the intervention group, even though only 6% of the patients initiated pharmacological treatment, the LDT exhibited a notably significant prolongation.

TFS reflects a constellation of clinical parameters, including LDT, eventually leading to the need for pharmacological treatment initiation. Pharmacological treatment imposes a burden of side effects, development of resistance, clonal evolution, and cost [27–31].

Twenty-five percent of patients participating in the RESONATE trial discontinued ibrutinib treatment due to side effects. Almost all patients suffered from side effects to some degree [30]. A similar frequency of side effects was observed in CLL 14 trial, which studied obinutuzumab plus venetoclax versus obinutuzumab plus chlorambucil as first-line therapy for CLL patients [31]. MBI was safe in this study and in previous studies using MBI, with no side effects related to the intervention. We have shown improved TFS in the intervention group, postponing the need for pharmacological treatment initiation.

Previous review [2] has indicated that intervening early in the disease and having a shorter duration of diseases are associated with more favorable results when employing MBI, consistently with our results. Intriguingly, it was observed that neither unmutated IgHV nor cytogenetic abnormalities, known to be associated with poor outcomes (mainly 17p deletion), influenced the beneficial impact of MBI.

We acknowledge several limitations in our study. This study was not randomized; therefore, we cannot rule out additional confounding factors. Nevertheless, the control and intervention groups were very well balanced in all study covariates. Patients choosing to participate in the intervention group may be more likely to engage in other health practices that might reduce stress-inflammatory responses and disease progression. These may include physical exercise, healthy nutrition, social engagement, and other relaxing activities. The willingness to participate in such an intervention program reflects a certain mindset and motivation, but in our opinion, does not weaken the results, but rather emphasizes the working premise. In previous studies, no correlation was found between personality and prognosis of cancer [32, 33]. Thus, the participants' basic personality characteristics are not expected to influence prognosis.

This particular MBI model has not been compared to other psychological or MBI techniques or placebos. It is worth noting that alternative intervention methods and approaches could hold potential benefits. However, these alternatives have primarily been explored in conjunction with conventional treatments like surgery, radiation, and pharmacological therapy [2]. Importantly, a placebo effect may be present in our study. Placebo effect has demonstrated efficacy in benign conditions like duodenal ulcers and Parkinson's disease. However, within the realm of cancer, it was shown to alleviate certain associated symptoms, such as fatigue, without influencing the overall course of the disease [34, 35]. Typically, placebo effects tend to diminish over time [36], while our study revealed that MBI impact was evident after 6 months, and became more pronounced as the study advanced.

The decision upon initiation of pharmacological treatment for CLL is based on defined guidelines. Nevertheless, there are gray areas in which a patient's preference plays a major role in this decision making. We cannot exclude the possibility that patients participating in the intervention group were less keen on starting pharmacological treatment. Yet, it was the MBI that prompted one of the patients from the intervention arm to accept the initiation of pharmacological treatment, which she previously denied.

Although the intervention program in this trial was relatively long, with a median duration of 18 months, longer follow-up is needed in order to assess the long-term effect of it, as well as to determine whether MBI can be applied for a certain time period or rather practiced continuously during the disease course. To conclude, we have shown that MBI, based on behavioral, cognitive, and spiritual processes, was associated with prolonged LDT and TFS in patients with CLL in the w&w phase.

This intervention should be further investigated in different types and stages of malignant diseases. It can also potentially serve as a prophylaxis measure, for example, in cases of high-risk Monoclonal Gammopathy of Unknown Significance (MGUS), aiming to prevent evolution to Multiple Myeloma. Longer follow-up is required, and a maintenance MBI protocol might be of benefit.

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Statement of Ethics

The study protocol was approved by Assuta Ethical Committee (0101-19-ASMC) and was registered at: https://my.health.gov.il/CliniTrials/Pages/MOH_2021-06-01_010011.aspx. All participants signed a written informed consent.

Conflict of Interest Statement

A.Z-L. served as a consultant for Sobi; however, this relationship does not bear any relevance to the content presented in this manuscript.

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"Flute of light" association for patients with hematologic malignancies in Israel funded the individual sessions of the intervention study. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Author Contributions

Shirley Shapira designed the study, conducted the study, and wrote the manuscript. Adi Zoref-Lorenz conducted the data analysis and helped prepare the manuscript. Naama Hirschberger was a co-investigator and helped with data collection. Yishai Ofran, Esti Mandel, and Noa Rabinowicz helped prepare the manuscript. Barak Mizrahi was responsible for data analysis and statistical analysis. Ohad Benjamini helped with data collection. All authors reviewed and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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