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Research paper

Controlled pilot study for cancer patients suffering from chronic fatigue syndrome due to chemotherapy treated with BioBran (MGN-3-Arabinoxylane) and targeted radiofrequency heat therapy

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The present scientific contribution is dedicated to the 650th Anniversary of the foundation of the University of Pécs, Hungary.

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ABSTRACT

Introduction: Although modern therapies for cancer have improved life expectancy, the management of disease and improvement of quality of life (QoL) of patients, especially managing cancer-related pain and chronic fatigue syndrome are still limited. *We demonstrate the efficacy of a combined therapy to treat cancer patients suffering from CFS.* The effects of a combined therapy in cancer patients suffering from CFS was evaluated. NK cells were stimulated, additional tumour treatment together with targeted radiofrequency therapy (Oncothermia).
Methods: SIXTY patients with CFS (due to suffering from any type of cancer) were recruited, (according to the Centres for Disease Control 1994 criteria) attending an outpatient specialist CFS service for controlled pilot study. A total of 25 participants were given oral BioBran (MGN-3-Arabinoxylane), + Oncothermia, for six months, equivalent control group has not received this complex (BioBran + Oncothermia) treatment, they received chemo-,radiotherapy treatment.
Results: The whole body pH status showed strong tissue acidity before the treatment, but the BioBran group changed the tissue pH status. The most important finding was that the average of CFQ score was significantly reduced after the treatment, and in control group the CFQ scores did not change significantly.
Conclusion: The findings support a specific therapeutic effect of the complex BioBran+ Oncothermia therapy in CFS of cancer patients improving their QoL, enhancing NK activity in synergy.

1. Introduction

Malignant tumours are the second leading cause of mortality all over the world [1], and. 44–45% of the population will be diagnosed with some type of malignant tumour during their lifetime [2]. Although modern therapies for cancer have as their focus to improve life expectancy, the management of this serious and complex disease [3] and improvement of quality of life (QoL) of patients, especially managing cancer-related pain and chronic fatigue syndrome are still limited. Cancer-related pain is frequently reported among patients, with 54% of patients experiencing pain [4]. The occurrence of pain in cancer patients increases the risk of psychological disorders (*e.g.*, anxiety, depression, and suicidal ideation) [5], and distract patients from their daily activities (*e.g.*, ability to concentrate); due to chemotherapy the so called chemo/brain and other side effects can influence the daily activity as well [6]. In addition, the cause of pain and CFS (Chronic Fatigue Syndrome), is not limited to the physiological aetiology of the disease, but also arises through side effects of treatment modalities like drugs, radiotherapy, and chemotherapy [3].

Chronic fatigue syndrome (CFS) is a complex and chronic condition, of unknown aetiology, which usually presents with post-exertion malaise and fatigue. People often experience disturbed sleep, cognitive difficulties and muscle weakness. There is no evidence based diagnostic test available for CFS. However, a number of research diagnostic criteria have been devised in order to offer consistency, reliability and comparison between research studies. Whilst there are a number of differences between each criteria, all suggest people must have debilitating fatigue for at

Abbreviations: CAM, complementary and alternative medicine; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; VAS, Visual analogue scale; QoL, quality of life; PGIC, Patient Global Impression of Change.

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least six months of new or definite onset, with other symptoms to include myalgia, mood and sleep disturbance [7–10]. The estimated prevalence of CFS ranges widely from 2 to 4900 per 100,000 people. Such estimates vary widely due to the diagnostic criteria used. CFS is three to four times more likely to affect women than men [7]. A systematic review looking at the treatment of CFS suggests that full recovery is rare [7–10]. However, an improvement in symptoms is more common than full recovery, with an average of 40% of people receiving systematic interventions reporting improvement of symptoms at follow-up. Despite this, the prognosis and chance to return to work is poor with a progression or worsening of illness over time being reported unless systematic intervention is received. Wide ranges of pharmacological treatments have been used for various aspects of CFS by clinicians. Pharmacological treatments used include *antidepressants, dopamine agonists, and analgesics.* Some previous reviews on pharmacological treatments have found to be inconclusive, insufficient or no evidence for the effects of these treatments in CFS [7–10]. In our study the efficacy of a combined therapy to treat cancer patients suffering from CFS was evaluated.

2. Methods

2.1. Interventions

1. BioBran (MGN-3-arabinoxylane) is a well-known food supplement. According to different CAM modalities it belongs to "biological food" supplementary therapy. Its active ingredient is *arabinoxylane*, a hemicellulose compound that is released from rice bran when it is incubated with an enzyme obtained from Shitake mushrooms. In recent study, we used 1000 mg sachets of BioBran. (Daiwa Pharmaceutical Co.Ltd, Tokyo, Japan) The preparation is identical to that sold over the counter by the manufacturer in Japan, UK, Europe and USA. The product received its Japan Health Food Authorization (JHFA) mark from the Japan Health Food and Nutrition Food Association in 1999 [11,12].
2. Oncothermia, i. e. the modulated electro hyperthermia system is a fast-developing supportive, complementary treatment method applied against different types of malignant tumours. The principles are based on the classical method of hyperthermia, but the aim, beside the absolute increase in temperature, is especially the direct electric-field energy absorption in the extracellular liquid and destroying the membrane of the cancer cells. Oncothermia's effect is synergic to radiotherapy and to numerous chemotherapies. Furthermore, it leads to an increased immunogenicity and effectively reduces the pain of the patient. Hyperthermia has been described as the "oldest identified weapon against cancer." It has been used since at least 1989.Oncothermia in general is not used as *sole therapy*. It is usually combined with chemotherapy, radiotherapy or other therapies and their combination. The method transfers energy using the principle of capacitive coupling (like a condenser) of radio waves of 13,56-MHz. Oncothermia utilizes the special absorption rate of the near-membrane extracellular liquid of the tumour. The tumour tissue has lower impedance than the surrounding tissues, so most of the transmitted energy is absorbed by the cancerous lesion. This selection of the tumour tissues (self-focusing) renders external focusing unnecessary. Oncothermia achieves a permanent increase of the temperature in the extracellular liquid of the tumour tissue. Due to the constant energy-supply, a temperature gradient (temperature difference) between the extra- and intracellular electrolytes develops until the thermal equilibrium is reached at the end of the therapy. This (in absolute numbers very low) temperature difference acts on the likewise small distance through the cellular membrane (from extra- to intracellular) and that leads to a destabilizing thermal stress on the membrane of the tumour cells, leading those into apoptosis [33].
3. CAM investigations: BETA-test for pH status, Enderlein 'dark-field' microscope test.
4. Questionnaires were completed every month by all patients: "Chalder Fatigue Scale" (CFQ), "Patient Global Impression of Change" scores, EORTC QLQ-C30 (version 3), VAS. We involved in the follow up checking procedure the followings, too: blood test especially focusing on *anaemia, neutropenia, monitoringgastrointestinal problems* (nausea, vomiting, weight loss, appetite loss, diarrhoea, constipation), ***neurological*** *side effects (*hand and foot-syndrome, peripheral neuropathy, Chemo Brain (memory), Tiredness), *endocrine side effects of chemotherapy* (hot flashes), dermatological *symptoms (hair), Basic quality of life (and changes to basic level).*

3. Procedure

3.1. Participant recruitment

Participants were recruited from outpatients attending a specialist CFS rehabilitation service: the Yamamoto Rehabilitation Institute, which is a practical tutorial centre of Pecs University Health Science Faculty. (Budapest, Hungary). 60 patients were chosen from the patient database of the Yamamoto Rehabilitation Institute based on the CDC criterion as randomised pilot study: suffering from any type of cancer (different stages), (treated by chemo- or radiotherapy), looking for additional CAM therapy as form of self-management of the situation.

Over a period of 6 months, 30 participants were fit the inclusion/exclusion criteria. Selected to take part in BioBran+ Oncothermy treatment and 30 participants for control group. Oncothermia (local heat) was performed 15 times during period with 1–1 h application per 15 weeks. This study incorporated specific inclusion and exclusion criteria for randomisation.

The participants had to have a confirmed diagnosis of cancer by an oncologist, and a baseline pain score of 3 or more on a 0–10 rating scale. The participants' pain was considered to be the consequence of the underlying cancer or cancer treatments. The participants were ambulatory and followed up, (6 months) the platelet count was 50,000/mL or greater, and *obtained permission from their physicians to participate in the study.*

Participants were excluded from the study if they were unable to obtain permission from their treating physicians, if they were unwilling to sign informed consent, or if they were involved in any current litigation. They were also excluded if they were simultaneously infected with HIV/hepatitis B virus, if they had neutropenia defined as an absolute neutrophil count of <1000/mL, or if they had any kind of bleeding disorders where the platelet count was $<50{,}000$/mL. Altogether 10 were excluded from above mentioned reasons.

Male and female patients with a diagnosis of CFS according to the Centre for Disease Control (CDC) 1994 criteria and suffering from cancer were included in the study. Other inclusion criteria were cancer duration of between 6 and 18 months, age >18 years and two or more of the following symptoms suggestive of immune activation: tender lymph nodes, sore throat or poor temperature control. Patients were excluded if they were taking immune-modulator medication, were unable to attend for out-patient appointments, or were pregnant or breast-feeding.

Permission to carry out the study was obtained from the Health Sciences Faculty of Pecs University (ethical permission: XIX. Szakrendelo Etikai bizottsagi hatarozat. 16/2015/17) approved this

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study. All eligible participants gave signed informed consent prior to clinical screening.

Prior to starting the trial the following tests were done: (1) *CAM diagnostics*: BETA-test, Enderlein dark field microscope test, (2) *Conventional diagnostics*: ECG, blood test (qualitative, quantitative, ions, protein, kidney and liver function), and (3) *Psychological tests*: Chalder Fatigue Scale questionaire (CFQ) and Patient Global Impression of Change (PGIC), and EORTC QLQ-C30 (version 3), VAS questionnaire [13–20]. In the period of treatment course we excluded 10 participants due different reasons, see flowchart. (Fig. 1). All of rest recruited 25 patients were treated with BioBran + Oncothermia and the other 25 patients – as a control group- were treated with chemo- or radiotherapy, as routin care during the study.

Oncothermia was given once a week (15 times) during the total course for 60 min with 140 W energy per each session applying local electrodes to the area of the tumour. At the end of the study (24th week) the diagnostic tests were repeated. Study packs contained sachets of BioBran MNG-3-arabinoxylane, and were identical in every way other than the study number marked on the outside. All patients were asked to take a dose of 1 g BioBran 3 times a day dissolved in water or milk for 24 weeks.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C3) and a visual analogue scale (VAS) for pain were used in this study. Both of these measures were shown to be valid and reliable for cancer patients [21–23]. The EORTC QLQ-C3 is a 30-item questionnaire used to assess health-related QoL, which includes five functional scales (physical, role, emotional, cognitive, and social) and eight single-item symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea). All functional and symptom scales are 4-point scales (*e.g.*, 1 = not at all to 4 = very much) with a total range from 0 to 100. A 7 – point scale from "very poor" to "excellent", assessed QoL. The descriptions of the scores are as follows: high functional scale score represents a high and healthy level of functioning; high general health status represents a high QoL; high symptom scale score represents a high level of symptomatology. A standard VAS was used to evaluate the participant's subjective perception of pain. Each participant was provided with a horizontal 100-mm line anchored with the descriptions "no pain" and "worst pain" at each end. The participants marked the line at their current levels of pain, and the evaluator used a ruler to measure the patients' marks. All participants were asked to complete both outcome measures at the beginning of the study, as well as at the end of weeks 4, 8, 12, 16, 20, 24. The participants were asked to fill the forms in prior to their treatments at each month. There was also an on-site follow up evaluation at 4 weeks after the last treatment (end of week 28). No information on participant–provider interactions or patient expectations was collected.

The study team evaluated both BioBran + Oncothermia treated patients and patients only treated with chemo- or radiotherapy (control group) to confirm equivalence.

In addition to researchers and participants, the database manager remained blinded until the analysis was completed. All patients are advised to maintain a natural healthy diet with an adequate intake of fruit and vegetables. No additional instructions on diet were given to participants in this study, and food intake was not monitored. NK cell activity was not measured directly by laboratory testing, as this was felt to be a costly addition to this trial that would not directly contribute to the main research objective of ascertaining whether *BioBran* and Oncothermia was effective in improving the symptoms of CFS in cancer patients.

3.1.1. Administration of outcome measures

The written instructions at the start of each self-report questionnaire instructed participants to report their current condition. Participants were asked to complete the questionnaires in private in order to reduce the influence of researcher expectations on the answers given.

3.2. Outcome measures, data analysis

3.2.1. Statistical analysis

All analyses were on an intention-to-treat basis, using the Statistical Package for Social Sciences (SPSS 11.5), a 5% significance level and two-tailed tests. The demographic characteristics of the patients were described using the mean and standard deviation (SD). The percentages of improvement from baseline in the VAS, and EORTC QLQ and general health status/QoL at the end of week 8,12,16,20, and the end of week 24 and 28 (after 4 weeks follow-up) were calculated for individual cases. The percentages were calculated by dividing the difference between the baseline and endpoint scores by the baseline score. The VAS and fatigue and general health status within the EORTC QLQ were presented as the mean ± SD. Values of $P < 0.05$ were considered statistical significant. A longitudinal regression analysis (random mixed-effects model) was also performed on an exploratory basis for each outcome measure to describe the overall trend and the rate of change over time (considering variations in the baseline values of all measurements) starting from baseline.

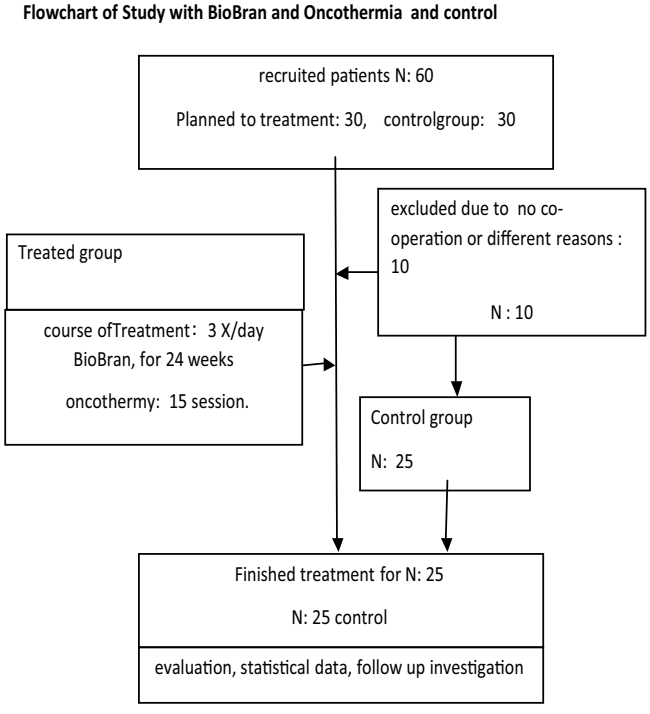

Fig. 1. Flowchart of Study with BioBran and Oncothermia and control.

4. Results

4.1. CAM diagnostics

BETA-test and Enderlein dark-field microscope test was done. The BETA (measurement of tissue pH) test was used to determine the full pH status of the whole body. Dark-field microscopy according to Enderlein claims to be able to detect disease at an early stage through minute abnormalities in the blood. In Germany and the USA, this method is used by an increasing number of

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Scale	BETA	Enderlein dark-field microscopy	Antioxidant
0	Healthy tissue pH	Healthy blood without any abnormalities	Extremely low
1	Minimal tissue pH	Almost healthy blood with some	Low
2	Medium stage	Medium stage	Medium
3	Low tissue pH	Slags and abnormal cells	Healthy
4	Extremely low tissue pH	Lot of slags and abnormal cells	-

Fig. 2. Beta test and Enderlein dark-field microscopy.

physicians and health practitioners, because this easy test seems to give important information about patients' health status. See Fig. 2.

We used five-stage score system to describe the blood status. The patients' antioxidant level was also determined before and after the treatment. The average of the BETA test score was 2.6 ± 0.2 and 1.1 ± 0.3 (before and after the treatment, respectively, $p < 0.01$). This data suggest that the whole body pH status showed strong tissue acidity before the treatment, but the BioBran + Oncothermia normalized the whole body pH status. The Enderlein dark-field microscopy test showed a lot of sludge ("slugging" and abnormal cells in the blood (average score is 2.7 ± 0.1) before the treatment, but the number of slag and abnormal cells are prominently reduced after the treatment (1.7 ± 0.1, $p < 0.01$, Fig. 3A and B).

Fig. 3A. The Enderlein dark-field microscopy test showed a lot of slags and abnormal cells in the blood (average score is 2.7 ± 0.1) before the treatment, but the number of slags and abnormal cells are extremely reduced after the treatment. (Fig. 3B)

It means the patients are much healthier after the BioBran + Oncothermia application. And finally the antioxidant status increased from the low level to normal (from 1.0 ± 0.01 to 2.7 ± 0.2, before and after the treatment, respectively, $p < 0.01$). There were no significant changes in the CAM tests data in control patients. Sixty participants were screened, and ten participants were excluded. Of the rest 50 participants, all successfully completed the study, later two dropped out because of natural progression and exacerbation of their diseases, of the 48 participants who completed the study, 28 were female and 20 were male. The median age was 66 years (range: 44–71 years). Fifteen of the 48 participants were diagnosed with breast cancer, and the other three were diagnosed with leukemia, non-Hodgkin's lymphoma, and pancreatic, prostate, liver cancer respectively. Percent improvements in emotional function and QoL * can be seen on Fig. 4 (Fig. 5). (according to CFQ questionnaire of 4th and 24th weeks.)

Mean scores of the general health status/QoL, VAS, and fatigue. (Fig. 6A). Percent improvements in the VAS, physical function, emotional function and QoL * can be seen on Fig. 6B altogether treated and non-treated data.

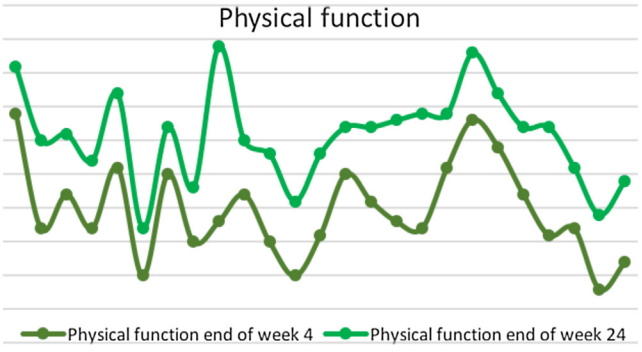

Fig. 4. Physical function on treated and untreated patients (dark green: untreated).

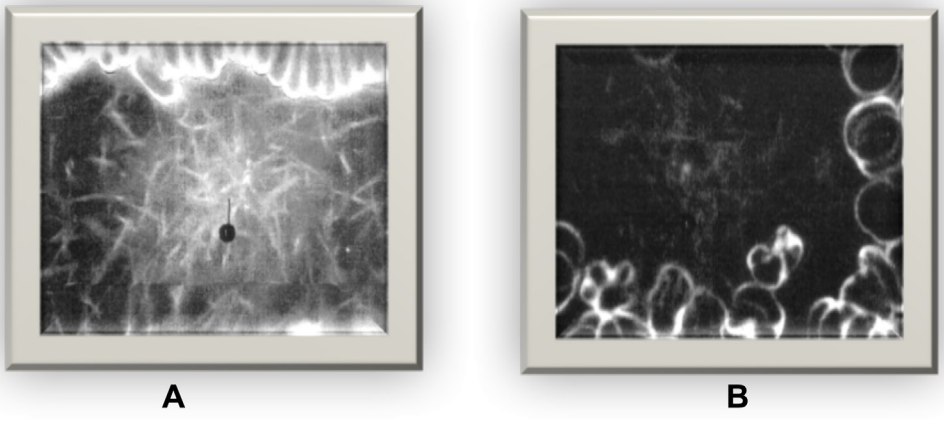

Fig. 3. A) Representative dark-field microscopy photos before (left) and after (right) B) the BioBran + Oncothermia.

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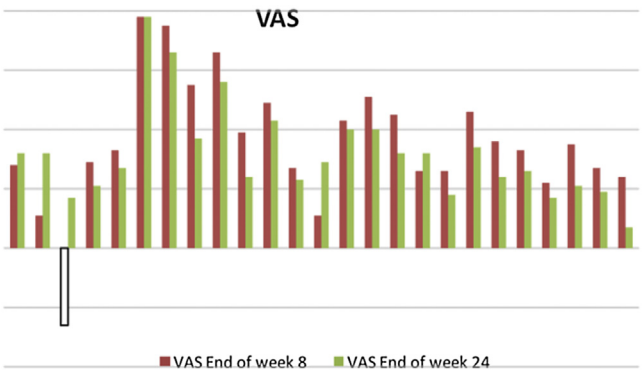

Fig 5. CFQ Questionnaire and physical activity, VAS scale *green treated, red untreated.

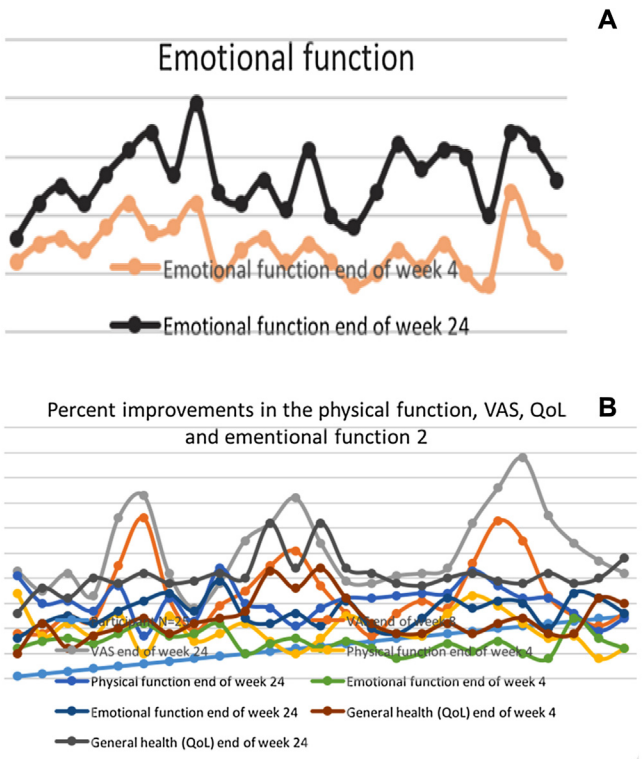

Fig. 6. A) Emotional function (black treated, red untreated). B) Improvement in physical function, emotional function, VAS, QoL.

4.2. Conventional diagnostics

ECG, blood tests (qualitative, quantitative, ions, protein, kidney and liverfunction parameters) were performed to determine the health status of patients. There were no CFS specific changes found, and there were no significant changes before and after the BioBran + Oncothermia or control group treatment.

4.3. Psychological tests

Chalder Fatigue Scale and Patient Global Impression of Change questionnaire, (EORTC QLQ-C3) and a visual analogue scale (VAS) were used to determine the psychological and wellbeing status and scores of the patients (Fig. 6B).

In the analysis the reduced numbers mean the patient feel itself more healthy or powerful. The most important finding was that the average score of CFQ questionnaire was 23.9 ± 2.3 points before the BioBran + Oncothermia treatment, but it was significantly reduced (14.6 ± 2.3) after the treatment. However, there were no significant changes after no treatment (CFQ is 23.2 ± 7.2, $p < 0.01$). The average PGIC score after the treatment was 2.1 ± 0.5 (means "much improved") which shows the patients felt the therapy could help to reduce the CFS symptoms. In no treated group the PGIC score was 4.3 ± 0.9 (means "no changes").

Changes can be seen in general health feeling of patients on Fig. 7.

5. Discussion

We investigated whether *BioBran with Oncothermia* application could improve the symptoms of CFS among cancer patients with symptoms suggesting immune involvement, using a pilot, controlled design. We believe that the use of this methodology has minimized the possibility of bias in the results. Our findings support the use *BioBran and Oncothermia* as a not only symptomatic treatment for CFS of cancer patients. In this combined therapy BioBran (MGN-3 Arabinoxylane) was applied for immune-stimulation targeted radiofrequency heat therapy (Oncothermia). Thermal stress was used to destabilize the membrane of the tumour cells, leading them into apoptosis and increasing the native bio stimulant action of BioBran to achieve balanced homeostasis of CFS patients. The rationale for this trial was based on previous published studies in CFS patients that appeared to demonstrate reduced NK cell activity and antioxidant level, and speculation that there might be an underlying immunological cause for CFS. In previous studies, BioBran had stimulated NK activity *in vitro* and *in vivo*, and so we hypothesized that our combined therapy might prove therapeutic outcome in some CFS patients. We did not measure NK cell activity directly, but focused instead on measuring symptomatic improvement in participants. [9,10,24–33]

A randomised controlled trial of 16 participants in 2003 found some correlation between improvement in CFS symptoms and increased NK cell activity in participants allocated to treatment with the immune-pharmacological agent isoprinosine[31]. However, McDermott and his colleagues in 2006 presented the effectiveness of a putative NK cell stimulant, BioBran, in reducing fatigue in CFS patients. While there may be an association between increased NK cell activity and improved CFS symptoms, no underlying mechanism for this has yet been defined, and the relationship remains unclear. McDermott and his colleagues performed a placebo-controlled, double-blind, randomised controlled trial of BioBran in CFS. Seventy one patients with CFS were given oral BioBran (1 g three times per day) or placebo equivalent for 8 weeks. Their findings did not support a specific therapeutic effect of BioBran in CFS. The improvement showed by both groups

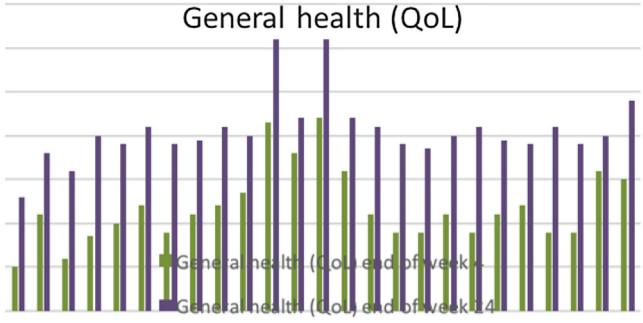

Fig. 7. General Health feeling of treated (black) and untreated (green) patients.

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over time highlights the importance of placebo controls when evaluating interventions in CFS. While McDermott and his colleagues could not demonstrate any effects of the CFS patients after BioBran application we improved the therapy and combined BioBran with targeted radiofrequency therapy [32]. This complex therapy was useful, because the whole body pH status of CFS patients showed strong tissue acidity, the Enderlein dark-field microscopy test showed a lot of slag and abnormal cells in the blood, and the antioxidant status was reduced before the treatment, but were normalized after the treatment. The most important finding that the average of CFQ and PGIC scores was significantly reduced after the treatment, and the control group *without BioBran+ Oncothermia* did not have any such an effects.

Our study also gave evidence that the conventional diagnostics and tests are not useful tool in the CFS diagnostic, however the CAM tests (e.g. dark-field microscopy and BETA-test) can provide healthcare professionals with help to monitor the effectiveness of the applied therapy in CFS in patients with cancer.

6. Limitation of the our study

However, the numbers of the participants are low in this randomised pilot study, but the data showed significant development after the BioBran + Oncothermia treatment. We believe based on these results we can perform a study with more participants, performing more tests and immunological laboratory investigation. Also we have not evaluated in this final results of recent study the improvement of tumour apoptosis proved by MRI, PET according published efficacy by us and other author of electro-hyperthermia [33].

7. Conclusion

In this pilot study, the results of the EORTC QLQ-C3 and QoL, VAS showed that complex treatment of immune stimulant BioBran + Oncothermia might be beneficial for reducing pain and improving QoL (as part of CFS syndrome) in cancer patients by enhancing NK cell activity as synergic mechanism and providing finally a better homeostasis. The synergy of BioBran and Oncothermy arise the possibility of forced I type immune system activity against malignant tumours. We founded useful additional treatment of the standardised MGN/3 BioBran in oncological patients. The combination of MGN-3–BioBran and Oncothermia promotes complete remission, which is rarely achieved with chemotherapy only.

The better glucose tolerance, the pancreas function (hormonal and digestive effect) function of liver, decreasing more side effects of necessary chemotherapy altogether result the better QoL of patients.

Competing interest

The authors declare that there is no conflict of interest with any financial organization regarding material discussed in this manuscript.

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