

Research Article

Effects of a Symbiotic on the Quality of Life of Elderly Patients with Breast Cancer: a Randomized Controlled Pilot Trial

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Abstract

Background: A number of studies have confirmed the beneficial effects of prebiotics and probiotics on several physical and psychological health outcomes. The present study aims to evaluate the feasibility, tolerance and preliminary results of a symbiotic, composed by oryzalose and *Lactobacillus plantarum* on sleep quality and psycho-physical stress in a group of elderly patients affected by hormonal dependent breast cancer.

Methods: A total of 40 patients with histologically proven breast cancer were randomly assigned to group A (intervention) or group B (placebo). Pittsburgh Sleep Quality Index (PSQI), Short Form Health Survey (SF-36) and HADS (Hospital Anxiety and Depression Scale) were submitted to all participants, provided an informed consent, at the enrolment and 6 months later.

Results: After treatment, the group A showed the highest SF-36 physical functioning and vitality score ($P=0,01$), the lowest bodily pain score ($P=0,01$) compared to the placebo control group. Group A achieved a significant improvement in the quality of life for all SF-36 domains. Moreover, the intake of symbiotic led to a significant improvement of several PSQI subscales (sleep quality, sleep disturbances, daytime dysfunction). There was a non-significant increased rate of participants classified as good sleepers. Decreased levels of anxiety and depression were observed in group A, but the difference was not significant.

Conclusion: According to our results, a combination of oryzalose and a probiotic could significantly improve both physical and psychological outcomes in a population of elderly breast cancer patients, with excellent safety profiles and optimal compliance.

Keywords: Quality of life, Psychological distress, Cancer, Microbiome, Oncobiotic

Introduction

The human microbiota is gaining more and more attention in the pathogenesis and management of several cancers, including breast cancer, within a new frame of science defined oncobiotic. As regards breast cancer, microbiome seems to be relevant for at least five reasons: the impact of dysbiosis on immune competence [1], systemic inflammation [2], hormonal milieu through the so called “estrobolome” [3-5], the emotional balance (psychobiotic) [6] and breast tissue microbial composition [7]. In fact, several studies have shown that breast tissue has a distinct microbiome with particular species enriched, and somewhat related to the gut bacteria through a gut-breast axis [8-9]. The question remains whether the microbiome plays a causal role in breast carcinogenesis or is an epiphenomenon; accordingly, probiotic treatment may be protective against the incidence of cancer and at least some of cancer related side effects [10]. The microbiome can also interfere with pharmacodynamics and efficacy of some anticancer treatment protocols, including chemotherapy and immunotherapy [11-14]. In addition, achieving benefits in terms of QoL has become increasingly important in

cancer treatment, with the traditional endpoint of survival deemed insufficient as the only treatment outcome [15]. Immune dysfunction leading to inflammation is the underlying mechanism that affects the patient physically and emotionally, which also has an indirect impact on social functioning [16]. Inflammation is a hall-mark of cancer as it is associated with the microenvironment of almost all tumor sites [17]. Persistent and localized inflammation can lead to the leaking of pro-inflammatory cytokines into circulation and trigger a systemic inflammatory cascade [18]. There is a consistent relationship between increasing systemic inflammation and worsening of all QoL parameters, such as global health, physical and social functioning, fatigue, pain [19]. Increased inflammation in the central nervous system also triggers behavioural co-morbidities, including depression, anxiety, fatigue, cognitive disturbances, and neuropathic pain. In the present study, we aim to study the feasibility and tolerance of a symbiotic supplement (Superbran) composed by a prebiotic molecule (Oryzalose, a polysaccharide derived from enzymatically treated rice bran with an extract of the shiitake mushrooms), in association with *Lactobacillus Plantarum*, a probiotic with proven efficacy in activating the cytokine TRAIL (Tumor Necrosis Factor-Related

Apoptosis Inducing Ligand), gamma-amino butyric acid (GABA) and anthocyanin in a population of elderly breast cancer patients. The secondary endpoint of this pilot randomized controlled trial is to evaluate the effects of this supplement on quality of sleep and quality of life of a sample of elderly breast cancer patients, compared to placebo. The health-related quality of life (QoL) of cancer patients includes the subjective perception of symptoms, as well as physical, emotional, social and cognitive functions, and the side effects of hormonal treatments [20].

Materials and Methods

This is a parallel, randomized, double-blind and placebo-controlled trial carried out at Fondazione Policlinico Universitario A. Gemelli IRCCS, Center for Integrative Oncology, in Rome and at International Institute of Psychoneuroendocrineimmunology (PNEI) in Milan. A total of forty (40) non-metastatic female patients, over the age of 65 (median age: 71 years, range 65-83), with histologically proven hormone-sensitive breast cancer (ER+ and/or PR+), undergoing adjuvant hormonal therapy (aromatase inhibitors) were recruited from May 2018 to December 2019. Only three (3) of total 40 patients did not finish the study due to previous comorbidities. Twenty (20) patients were randomly assigned to the intervention group (A) and twenty (20) to the placebo group (B), matched by age and performance status. Informed consent was obtained from all the patients. The eligibility criteria were as follows: histologically proven hormonal responsive breast cancer, no ongoing corticosteroids therapy due to their immunosuppressive effects, and no concomitant treatment with other immunomodulating agents, such as interferons, interleukins and monoclonal antibodies. In both arms, supplement and placebo, supplied by PneiPharma (Milan, Italy), were administered orally in a three times/day dose for six months. At the enrolment, patients were asked to collect venous blood at 0 (baseline) and 6 months later, in the morning after an overnight fast. In each blood sample, we counted lymphocytes, monocytes and some lymphocyte subpopulations, including TH lymphocytes (CD4), cytotoxic T lymphocytes (CD8), T reg (CD4+CD25+), NK cells (CD16+CD56). Data were reported as mean ± SE, and statistically analyzed by the Chiquare test, the Student's test, and the coefficient of correlation, as appropriate. Moreover, we measured patients' symptoms of depression and anxiety using the Hospital Anxiety and Depression Scale (HADS), including 14 items rated on a 4-point Likert-type scale (higher scores indicate more severe symptoms). The PSQI (Pittsburgh Sleep Quality Index Malay Version) is a standardized, self-administered questionnaire that evaluates retrospective sleep quality and disturbances within the past month. It includes 19 items forming seven subscales: (1) sleep quality (1 item), (2) sleep latency (2 items), (3) sleep duration (1 item), (4) sleep efficiency (3 items), (5) sleep disturbance (9 items), (6) sleep medication (1 item), and (7) daily dysfunction (2 items). The PSQI was evaluated following the original scoring system. Each component has a score ranging from 0 to 3. The scores of seven components will be added up to get a total PSQI score ranging from 0 to 21. Respondents with an overall score above 5 are classified as 'poor sleepers', while those with a score of 5 or below are classified as 'good sleepers'. The SF-36 (Short Form Survey) measures 8 QOL domains which are dichotomized in physical (functioning, physical role limitations, pain, general health) and mental health (vitality, social functioning, emotional role limitations and

emotional/mental health) [21]. Item scores were converted to a scale of 0–100 points; the domain scores were derived by averaging individual items within the subscale; and physical and mental health composite scores were derived by averaging the four component domains of each one. Higher values are indicative of better QOL.

All the questionnaires were administered at 0 (baseline), 3 and 6 months in all the participants.

Results

The patients both in the intervention and in the placebo group tolerated well the treatment, did not report any remarkable side effect and only three drop out was recorded. The clinical characteristics of the evaluable patients are reported in Table 1. A clear relief from asthenia was achieved by patients enrolled in the intervention group (83%).

Improvements in QOL (SF-36) scores were reported at 3 and 6 months (Table 2), particularly in physical functioning, role limitations and pain, while the components of mental health QOL that improved more significantly were vitality and social functioning. Tables 3 and 4 report the results of groups A and B, respectively, for each domain of the SF-36.

Table 1: Subjects' characteristics.

	GROUP A	GROUP B (PLACEBO)
Age, Years, Mean (SD)	70 (65-78)	73 (67-83)
Height (m)	1.57	1.61
Weight (kg)	70,64	73,86

Table 2: The SF-36 score of the 2 groups at baseline, at 3 and 6 months.

	GROUP A	GROUP B	P*
SF-36 (WEEK 0)	50.3 ± 11.24	49.6 ± 9.3	0.001
SF-36 (WEEK 12)	53.3 ± 7.03	46.5 ± 11.24	0.001
SF-36 (WEEK 24)	55.4 ± 8.1	47.69 ± 10.8	0.001

Table 3: SF-36 domains in group A.

SF-36	0 month	3 month	6 months
Physical functioning	40.0 [20.0; 60.0]	47.5 [43.0; 65.0]*	52.5 [45.0; 61.0]*
Physical role	25.0 [00.0; 50.0]	30.5 [02.0; 120.0]*	37.5 [00.0; 100.0]
Bodily pain	31.0 [22.0; 41.0]	38.5 [38.0; 42.0]*	41.5 [41.0; 50.0]*
General health	48.5 [22.0; 77.0]	50.0 [42.0; 72.0]	52.0 [43.0; 62.0]
Vitality	27.5 [15.0; 40.0]	35.0 [30.0; 40.0]*	45.0 [40.0; 60.0]*
Social function	50.0 [25.0; 75.0]	53.5 [50.0; 65.0]	55.5 [50.0; 75.0]
Emotional role	33.3 [00.0; 66.7]	33.3 [00.0; 100.0]	33.3 [00.0; 100.0]
Mental health	60.0 [28.0; 76.0]	66.0 [48.0; 78.0]*	72.0 [55.0; 80.0]*

*Statistically significant (p=0.001).

Table 4: SF-36 domains in group B.

SF-36	0 month	3 months	6 months
Physical functioning	38.0 [20.0; 60.0]	40.5 [43.0; 65.0]	40.5 [45.0; 61.0]
Physical role	27.0 [00.0; 50.0]	30.5 [02.0; 120.0]	31.5 [00.0; 100.0]
Bodily pain	29.0 [22.0; 41.0]	30.5 [38.0; 42.0]	33.5 [41.0; 50.0]
General health	50.5 [22.0; 77.0]	52.0 [42.0; 72.0]	52.0 [43.0; 62.0]
Vitality	30.5 [15.0; 40.0]	33.0 [30.0; 40.0]	34.0 [40.0; 60.0]
Social function	47.0 [25.0; 75.0]	47.5 [50.0; 65.0]	46.5 [50.0; 75.0]
Emotional role	31.3 [00.0; 66.7]	33.3 [00.0; 100.0]	32.3 [00.0; 100.0]
Mental health	58.0 [28.0; 76.0]	60.0 [48.0; 78.0]	61.0 [55.0; 80.0]

There were no significant differences between group A and group B in mean HADS-A or HADS-D scores at baseline or during follow-up. However, after three months of follow-up there was a trend towards a reduction in the mean HADS-A score in group A compared to group B, resulting in a significant difference in mean change: -0.9 (-1.8, -0.01) in group A versus 0.5 (-0.4 to 1.4) in group B, $p = 0.02$. Moreover, after 6 months of follow-up the HADS-D scores remained stable in group A, but tended to increase in group B, resulting in a significant difference in the variation of score mean during this period: 0.05 (-0.8, 0.9) in group A versus 1.0 (0.3 - 1.8) in group B ($p = 0.03$) (Table 5). Significant improvements were also observed in the PSQI score of the both study groups but in group A the difference was statistically significant ($p = 0.002$) (Figure 1).

Discussion

Rice bran oryzalose exerts immunomodulating effects, which include upregulation of natural killer (NK) cell activity, increase of phagocytic cell functions, modulation of cytokines production and promotion of T and B lymphocyte proliferation [22]. The remaining components that are resistant to digestion serve as prebiotics for the gut microbiota, which induces anti-inflammatory and immunomodulatory effects and influence behavioral changes across the gut-brain axis. Among the large number of natural agents derived from plants and employed in the integrative management of cancer patients, oryzalose is extremely promising, due to its effectiveness in improving the clinical status of patients [23-26]. QoL improvements (sleep, appetite, digestion, physical activity, anxiety and pain), as well as reduced adverse effects during cancer therapy, have been reported in several studies [27-35]. Supplementing with oryzalose (400 mg/die) for three months also significantly enhanced the QoL scores of healthy elderly adults in a randomized controlled trial [36]. Clinical research on the effects of oryzalose in cancer patients is still in its early

stage [37-39], and most of the trials have several limitations, unclear risks of bias, non-validated QoL measurements [40,41]. Furthermore, none of these trials attempted to rule out the impact of placebo in QoL results. The gut microbiota is achieving increasing attention as a powerful regulator of quality of life, sleep and psychological outcomes in cancer patients; moreover, microbiome composition may be modulated by diet, exercise, behaviours, xenobiotics and probiotics [42-46]. Among the most studied and widely used probiotics, *Lactobacillus plantarum* is an excellent candidate for supplementation, due to its resistance to many classes of antibiotics and anti-inflammatory properties [47]. In this study, we aimed at assessing the effect of the prebiotic oryzalose in association with the probiotic *Lactobacillus Plantarum* in the management of cancer-related side effects and quality of life of breast cancer patients undergoing hormonal therapy. Several limitations of our study require consideration. First, we carried out this study in only two academic cancer center, in a sample of patients with limited racial and ethnic diversity; therefore, our findings cannot be generalized to other more heterogeneous populations. In addition, the short-term follow-up of the enrolled patients could be considered as another limitation of the study. One of the major strengths of the study is the advanced age of the population enrolled (over 65), who are usually excluded from clinical trials, despite being the most affected by the disease, due to the complexity of clinical issues [48]. Despite this, our drop out rate and participants compliance to the protocol were excellent, showing high profiles of safety for the compound under investigation. The results of this feasibility trial will inform the planning of a larger clinical trial for definitive conclusions.

Conclusion

This study showed an excellent compliance to the protocol of treatment and, as preliminary results, improved quality of life in terms of physical functioning, pain, vitality and psychological well-being in elderly breast cancer patients in the treatment arm compared to placebo. Further similar studies with longer follow-up periods in breast cancer patients are warranted in order to explore the impact of symbiotics and other modulators of patients' microbiome on cancer-related symptoms and quality of life, even in elderly populations due to the high adherence and safety profile of the prebiotic and probiotic treatment.

Conflict of Interest

The authors declare they have no competing interests.

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Table 5: Mean HADS score in the 2 groups before and after oryzalose.

	GROUP A	GROUP B
HADS-A (WEEK 0)	6.5 (5.46 to 7.4)	6.0 (6.7 to 7.5)
HADS-D (WEEK 0)	6.1 (5.4 to 6.7)	6.0 (5.5 to 6.5)
HADS-A (WEEK 12)	6.3 (5.8 to 6.8)	6.2 (6.8 to 7.6)
HADS-D (WEEK 12)	5.9 (5.3 to 6.5)	6.0 (5.8 to 6.8)
HADS-A (WEEK 24)	6.0 (5.5 to 6.5)	6.3 (6.7 to 7.3)
HADS-D (WEEK 24)	5.7 (5.3 to 6.4)	6.2 (5.6 to 6.6)

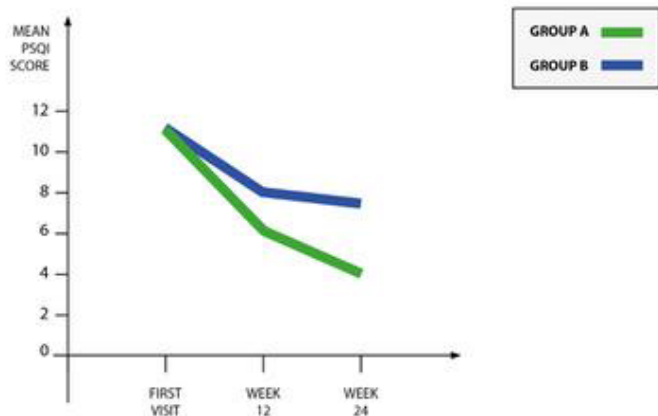


Figure 1: Mean PSQI score in the 2 groups.

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