A pilot surveillance investigation on the influence of a probiotic combination on side-effects caused by common anti-cancer therapies

L. Drago[1*], G. Meroni[2], D. Pistone[1,3], S.E. Aragona[4], F. Marampon[5], G. Rodà[6], G.V. Zuccotti[3,7], V. Tombolini[5] and the Oncobiota Group[#]

[1]Department of Biomedical Sciences, University of Milan, Milan, Italy; [2]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; [3]Pediatric Clinical Research Center "Invernizzi", Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy; [4]Centre of Regenerative Medicine, Humanitas Mater Domini, Castellanza, Varese, Italy; [5]Department of Radiotherapy, Policlinico Umberto I, Sapienza University, Roma, Italy; [6]Oncology Unit, Humanitas Mater Domini, Varese, Italy; [7]Department of Pediatrics, Children's Hospital Vittore Buzzi, University of Milan, Milan, Italy

[*]**The Oncobiota Group**: Aiello Dario, Amari Maria Laura, Andreozzi Francesca, Daidone Antonino, D'Alessio Adele, Della Vittoria Scarpati Giuseppina, Giarratano Giuseppe, Leo Silvana, Ombrosi Laura, Sasso Nicola, Spagnoletti Ilaria

***Objective*: This study aimed to investigate the possible reduction of the side effects caused by cycles of anti-cancer therapies using a probiotic combination of *Lacticaseibacillus rhamnosus* LR04 (DSM 16605), *Lactiplantibacillus pentosus* (formerly *Lactobacillus pentosus*), LPS01 (DSM 21980), *Lactiplantibacillus plantarum* (formerly *Lactobacillus plantarum*) LP01 (LMG P-21021), *and Lactobacillus delbrueckii subsp. delbruekii* LDD01 (DMS 22106).**

***Methods*: 180 patients were enrolled and grouped into four categories according to different cancers: breast (n = 38), lung (n=22), colon (n=55) and prostate (n=65). They received the probiotic combination with the first anti-cancer cycle (T0) for 30 days (T1) and reported the symptoms (nausea, vomit, etc.) using an absent-to-severe score.**

***Results*: Patients with prostate cancer registered a marked reduction in some symptoms after receiving the probiotic combination. Intestinal-related disorders showed a statistically significant decrease during the use of the probiotic (30 days). Nausea and vomit were reduced from 32.3% to 2.1% ($p<0.0001$), intestinal swelling from 53.8% to 21.6% ($p<0.01$), mucositis from 29% to 0 ($p<0.001$), diarrhea decreases from 38.4% to 8.1% ($p<0.001$), abdominal pain was reduced from 44.6% to 10.8% ($p<0.001$) and constipation from 40% to 13.5 % ($p<0.05$). Patients with colon cancer reported a decreased intestinal swelling over time (54.4% - 38.4%, $p<0.05$). No statistical differences were found in the two last groups (breast and colon cancer) for all the symptoms after introducing the probiotic.**

***Conclusion*: With a continuous focus on safety, a specific probiotic combination in contrasting the side effects of the anti-cancer therapies for the four different cancers here analysed should be considered. This pilot investigation was expected to provide only general indications that must be further validated with numerically larger studies and under more strict parameters.**

keywords: anti-cancer therapy, probiotics

Corresponding Author:
Prof. Lorenzo Drago
Department of Biomedical Sciences,
University of Milan,
Milan, Italy
e-mail: lorenzo.drago@unimi.it

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Gastrointestinal toxicity is one of the most frequent side effects caused by anti-cancer therapies (1, 14, 21). In addition, chemo- and radiotherapy can cause severe and debilitating intestinal damages, which can clinically lead to diarrhea, mucositis, and inflammatory (or ulcerative) alteration of the gastrointestinal mucosa (17, 19).

Anti-cancer therapies are also responsible for a long series of additional side effects such as nausea and vomiting, hair loss, constipation, and cutaneous pigmentary changes (4, 12, 13). In addition, vascular, dermatologic, endocrine, immunologic, and pulmonary toxicities have emerged for targeted cancer therapy (8).

The oncological patient is, by definition, a chronic patient who must undergo both antineoplastic and supportive cycles of therapy. Therefore, the main objective of clinicians is to contrast the numerous undesirable side effects caused by anti-cancer treatments and the development of more effective, less detrimental, and patient-specific therapies (24, 25).

Recent studies investigated the possibility of targeting microbiota components to enhance anti-cancer treatment efficacy while preventing toxicity; in this panorama, probiotics represent one of the most promising and valuable intervention tools (11, 22).

Probiotics are known to modify and protect the intestinal microbiota exerting a contrasting action on pathogens adhesion, enhancing mucosal barrier function, modulating the innate and adaptive immune response, and secreting bioactive metabolites (10). They have a beneficial role in diverse severe conditions such as inflammatory bowel diseases, multiple sclerosis, and rheumatoid arthritis (3, 6, 7, 15, 26).

An ever-growing number of studies show that probiotics might be implicated in protecting and maintaining the functionality of the intestinal microbiota with a positive outcome on cancer prevention, onset, and progression (5, 9, 23, 27). In addition, regular consumption of oral probiotics has been positively linked with the clinical efficacy of anti-cancer treatments and the capacity to mitigate the adverse and even life-threatening side-effects of chemo- and radiotherapy (18).

This study aimed to measure the probiotics' capacity in limiting the toxicity and reducing the severity of some common symptoms caused by the conventional anti-cancer treatments.

MATERIALS AND METHODS

Study design

Data were collected throughout a survey. A specific questionnaire was dispensed to each patient who answered the questions in a self-reported document deposited in an online electronic repository of data managed by Medical Doctors (MDs). The Information was collected from MDs together with the anamnestic and clinical status. This study represents a data collection that can be considered a preliminary step to plan a subsequent clinical trial. This type of study does not require Ethical approval according to Italian law; however, it had been approved by the Authorship Internal Board, which included several oncologists. Informed consent has also been requested from the patients during the first visit. The biases and limitations of this type of study have been considered and broadly discussed in the text.

Questionnaire and outcome

Patients included in this study were diagnosed with different cancers and grouped according to the tumour location: breast (n =38), lung (n =22), colon (n=55), prostate (n=65). All these individuals (n = 180) were at the beginning of the anti-cancer treatment when enrolled (T0). The patients were subjected to different therapies: chemotherapy, radiotherapy, immunotherapy, hormone and target therapy.

This study aimed to evaluate whether the daily administration (as recommended by the manufacturer's instructions) of the probiotic combination "Abivisor" (AURORA Biofarma, Milan, Italy) containing *L. rhamnosus* LR04 (DSM 16605; >=10^9 Colony Forming Units/ Active Fluorescence Unit [CFU/AFU]), *L. pentosus* LPS01 (DSM 21980; >= 8×10^8 CFU/AFU), *L. plantarum* LP01 (LMG P-21021; >=3×10^9 CFU/AFU), and *L. delbrueckii* subsp. delbruekii LDD01 (DMS 22106; >= 2×10^8 CFU/AFU) with N-acetylcysteine, recommended at a >= 5×10^9 CFU/AFU per day, or in combination with standard anti-cancer therapy for 30 days could clinically improve the adverse symptoms associated with the anti-cancer treatments. Each strain used in the probiotic is patented by Probiotical SpA (Novara, Italy) and selected for gastric pH tolerance and

synergy. Each patient delivered the scheduled self-reporting sheets during the first visits (T0-time of enrolment) and one month later (T1). The probiotic was administered upon enrolment (together with anti-cancer therapy); moreover, all the subjects signed the informed consent and privacy. The participation in the survey was on a volunteer basis, and the reasons behind patient withdrawal can be diverse (e.g., improvement or worsening of their health condition; surgeries or other treatments incompatible with probiotic administration; transfer to other facilities). The drop-out was generally independent of the probiotic treatment; no opportunistic infections were registered due to the probiotic combination intake or other adverse reactions.

The primary outcome focused on evaluating the presence and severity of specific clinical symptoms at the beginning (T0) and the end of the study (T1). The symptoms considered were: 1) burning epigastric pain, 2) nausea and vomiting, 3) belching flatulence and borborygmi, 4) intestinal swelling, 5) aphthosis and halitosis, 6) mucositis of esophagus and stomach, 7) mucorrhea, 8) colitis, 9) fatigue, 10) hydroelectric alterations, 11) diarrhea, 12) recurrent abdominal pain, 13) constipation, 14) dehydration needs, 15) cutaneous dyschromia, 16) cutaneous alterations. The severity of clinical symptoms was self-reported by patients using a progressive multiple choices questionnaire with three options: mild, moderate, and severe. The symptoms were considered absent when not included in the previous categories.

Statistical analysis

Statistical analyses were performed by *Chi*-square test and Fisher's exact test comparing the severity of symptoms at T0 and T1. The comparison was made by several patients reporting specific symptoms as mild, moderate, or high. A *p-value* less than 0.05 was considered statistically significant. The statistical analysis and graphic representation were performed with GraphPad Prism version 8.01 for Windows (GraphPad Software®, San Diego, USA, www.graphpad.com).

RESULTS

Overall data

The study enrolled 180 patients divided in four different categories depending on cancer types: breast (n = 38), lung (n=22), colon (n=55), prostate (n=65). The drop-out is consistent since 86 patients (47.4%) decided not to undergo the second visit at the end of the survey (T1). Safety issues remain of key importance, considering certain cancer patients' weakened and immunocompromised health status. Negative effects due to the utilisation of the probiotic were never reported. Chemotherapy, radiotherapy, immunotherapy, hormone therapy and target therapy for each cancer type administered before and during this study are reported in Table I.

Main outcomes

In patients with prostate cancer, the overall symptoms of nausea and vomiting decreased from 30.7% at T0 to 2.7% at T1 ($p<0.001$). Eructation, flatulence and borborygmi were reduced from 36.9% to 10.8% ($p<0.01$). The intestinal swelling decreased from 61.5% to 21.6% ($p<0.001$).

The prevalence of patients reporting aphthosis and halitosis decreased from 27.6% at T0 to 2.7% at T1 ($p<0.01$). Diarrhea was reduced from 38.4% at T0 to 8.1% at T1 ($p<0.001$) and abdominal pain from 44.6% at T0 to 10.8% at T1 ($p<0.001$). The percentage of

Table I. *Anticancer treatment prescribed to each patient included in this pre-clinical study.*

Cancer location	CT	RT+CT	RT	HT	TT	IT	Others
Breast (N=38)	14 (36.9%)	1 (2.6%)	4 (10.6%)	5 (13.1%)	2 (5.3%)	1 (2.6%)	11 (28.9%)
Lungs (N=22)	10 (45.4%)	2 (9%)	0	1 (4.5%)	0	3 (13.6%)	6 (27.3%)
Colon (N=55)	32 (58.2%)	4 (7.3%)	3 (5.4%)	0	3 (5.4%)	0	13 (23.7%)
Prostate (N=65)	2 (3.1%)	0	36 (55.4%)	19 (29.2%)	3 (4.6%)	0	5 (7.7%)

*Abbreviations: **RT**= Radiotherapy; **CT**= Chemotherapy; **RT**+**CT**; **HT**=Hormone therapy; **TT**= Target therapy; **IT**= Immunotherapy*

individuals reporting constipation decreased from 40% at T0 to 13.5% at T1 ($p<0.05$). Dehydration was reduced from 24.6% at T0 to zero% at T1 ($p<0.001$).

After using the probiotic combination for 30 days (T1), the overall number of patients reporting moderate and severe symptoms decreased. Only one patient reported nausea and vomiting at T1; statistically significant differences were found at a mild level, reducing from 26.1% to 2.7% ($p<0.01$). Eructation, flatulence and borborygmi showed a statistically significant difference at a moderate level, from 50% to 0 ($p<0.01$). Intestinal swelling was reduced to zero from a rather high-moderate (42.8%) and severe (22.8%) levels ($p<0.0001$ and $p<0.05$, respectively). Patients reported mucositis only at a moderate level, reducing from 100% at T0 to zero at T1 ($p<0.001$). The only statistically significant difference was at a moderate level for colitis, with a reduction from 25% at T0 to zero at T1 ($p<0.05$). A difference in hydroelectric alteration was reported at T0, at a mild level (93.3%), which was reduced to zero at T1 ($p<0.001$). Diarrhea decreased at a moderate level from 52% at T0 to zero ($p<0.001$). Abdominal pain decreased at a moderate level from 51.7% at T0 to 50% ($p<0.05$). Dehydration was reduced at a mild level from 93.7% at T0 to zero ($p<0.05$). Alteration of skin annexe was reported at a mild level, reducing from 100% at T0 to zero at T1 ($p<0.01$). For a comprehensive overview, including non-significant results, refer to Table II.

In the colon cancer group, the symptoms of intestinal swelling decreased from 54.5% at T0 to 38.4% at T1 ($p<0.05$). After using the probiotic for 30 days, the patients reported a decreased prevalence of symptoms at moderate and severe levels, but the differences with T0 are rarely significant. On a couple of occasions, we also noticed an increase in the severity of the symptom. The prevalence of patients reporting burning epigastric pain at a severe level increased from zero to T0 to 23.2% at T1 ($p<0.05$). The prevalence of mild symptoms for fatigue increased from 20.8% at T0 to 57.2% at T1 ($p<0.05$). For a comprehensive overview, including non-significant results, please refer to Table III.

In the remaining two groups (breast cancer and lung cancer), there were no statistically significant differences for all the considered symptoms between T0 (enrolment and beginning of probiotic administration) and time T1 (end of the study).

DISCUSSION

Anti-cancer therapies cause severe side effects to patients, including gastrointestinal dysbiosis (30). However, several clinical trials have highlighted the efficacy of using probiotics for reducing general discomfort and specific side-effects in cancer patients under anti-cancer treatment, therefore, improving the general clinical conditions and health status of such patients (29).

Among the most drastic gastrointestinal side-effects, often associated with anti-cancer treatments, diarrhea and mucositis are two common symptoms that can often be alleviated using oral probiotics (2, 20, 31).

In this study, we reported positive effects of the probiotic on patients affected by two different types of cancer: prostate and colon. In addition, statistically significant results were observed between T0 (enrolment) and T1 (end of the study), with a marked amelioration of some symptoms' severity.

For patients affected by prostate cancer, there was a consistent reduction ($p< 0.001$-0.0001) of nausea and vomiting, intestinal swelling, diarrhea and abdominal pain at moderate and/or severe levels after 30 days of using the probiotic combination. The cancer patients affected by nausea and vomiting, eructation, flatulence and borborygmi, constipation, colitis, and fatigue seem to receive some benefits, but the difference was less significant ($p< 0.05$-0.01). The remaining four symptoms (burning epigastric pain, mucorrhea, fatigue and dyschromia) seem not to receive benefits after using probiotics.

For patients diagnosed with colon cancer, intestinal swelling was the only symptom that showed a consistent reduction from 54.5% at T0 to 38.4% ($p< 0.05$). Remarkably, there are two cases in which the specific symptoms worsened after using the probiotic for 30 days. A statistically significant increase was registered for burning epigastric pain at severe level (3 patients 23.2% at T1 compared to zero at T0) and fatigue at mild level (from 20.8% at T0 to 57.2% at T1, $p<0.05$). The remaining symptoms (epigastric burning pain, belching, flatulence and borborygmi, aphthosis and

Table II. *The number, prevalence, and severity of specific symptoms for patients with different prostate* cancers.

Symptoms	Prevalence T0 (%)	Prevalence T1 (%)	*p*-value
PROSTATE CANCER	N = 65	N = 37	
Burning epigastric pain	29 (44.6%)	11 (29.7%)	Ns
Mild	15 (51.7%)	8 (72.2%)	Ns
Moderate	11 (38%)	3 (27.8%)	Ns
Severe	3 (10.3%)	0	Ns
Nausea and vomiting	20 (30.7%)	1 (2.7%)	P<0.001
Mild	17 (85%)	1 (100%)	P<0.01
Moderate	3 (15%)	0	Ns
Severe	0	0	Ns
Eructation, flatulence and borborygmi	24 (36.9%)	4 (10.8%)	P<0.01
Mild	9 (37.5%)	4 (100%)	Ns
Moderate	12 (50%)	0	P<0.01
Severe	3 (12.5%)	0	Ns
Intestinal swelling	40 (61.5%)	8 (21.6%)	P<0.001
Mild	17 (48.6%)	8 (100%)	Ns
Moderate	15 (42.8%)	0	P<0.0001
Severe	8 (22.8%)	0	P<0.05
Aphthosis and halithosis	18 (27.6%)	1 (2.7%)	P<0.01
Mild	11 (61.1%)	1 (100%)	Ns
Moderate	6 (33.3%)	0	Ns
Severe	1 (5.6%)	0	Ns
Mucositis	16 (24.6%)	0	P<0.001
Mild	16 (100%)	0	P<0.001
Moderate	0	0	Ns
Severe	0	0	Ns
Mucorrhea	5 (7.6%)	1 (2.7%)	Ns
Mild	0	0	Ns
Moderate	2 (40%)	1 (100%)	Ns
Severe	3 (60%)	0	Ns
Colitis	28 (43%)	11 (29.7%)	Ns
Mild	19 (67.8%)	9 (81.8%)	Ns
Moderate	7 (25%)	0	P<0.05
Severe	2 (7.2%)	2 (18.2%)	Ns
Fatigue	30 (46.1%)	19 (51.3%)	Ns
Mild	13 (43.3%)	13 (68.4%)	Ns
Moderate	13 (43.3%)	2 (10.5%)	Ns
Severe	4 (13.4%)	4 (21.1%)	Ns
Hydroelectric alterations	15 (23%)	0	P<0.001
Mild	14 (93.3%)	0	P<0.001
Moderate	1 (6.7%)	0	Ns
Severe	0	0	Ns
Diarrhea	25 (38.4%)	3 (8.1%)	P<0.001
Mild	11 (44%)	3 (100%)	Ns
Moderate	13 (52%)	0	P<0.001
Severe	1 (4%)	0	Ns
Abdominal pain	29 (44.6%)	4 (10.8%)	P<0.001
Mild	15 (51.7%)	2 (50%)	P<0.05
Moderate	13 (44.8%)	2 (50%)	Ns
Severe	1 (3.5%)	0	Ns
Constipation	26 (40%)	5 (13.5%)	P<0.05
Mild	14 (53.8%)	3 (60%)	Ns
Moderate	10 (38.4%)	2 (40%)	Ns
Severe	2 (7.8%)	0	Ns
Dehydration	16 (24.6%)	0	P<0.001
Mild	15 (93.7%)	0	P<0.001
Moderate	1 (6.3%)	0	Ns
Severe	0	0	Ns
Dyschromia	15 (23%)	4 (10.8%)	Ns
Mild	14 (93.3%)	4 (100%)	Ns
Moderate	1 (6.7%)	0	Ns
Severe	0	0	Ns
Alteration skin annex	14 (21.5%)	0	P<0.01
Mild	14 (100%)	0	P<0.01
Moderate	0	0	Ns
Severe	0	0	Ns

Table III. *The number, prevalence, and severity of specific symptoms for patients with different colon cancers.*

Symptoms	Prevalence T0 (%)	Prevalence T1 (%)	*p*-value
COLON CANCER	N = 55	N = 26	
Burning epigastric pain	16 (29.1%)	13 (50%)	Ns
Mild	8 (50%)	8 (61.5%)	Ns
Moderate	8 (50%)	2 (15.3%)	Ns
Severe	0	3 (23.2%)	P<0.05
Nausea and vomiting	22 (40%)	12 (46.1%)	Ns
Mild	11 (50%)	10 (83.3%)	Ns
Moderate	10 (45.5%)	2 (16.7%)	Ns
Severe	1 (4.5%)	0	Ns
Eructation, flatulence and borborygmi	17 (30.9%)	9 (34.6%)	Ns
Mild	7 (41.2%)	4 (44.4%)	Ns
Moderate	10 (58.8%)	3 (33.3%)	Ns
Severe	0	2 (22.3%)	Ns
Intestinal swelling	30 (54.5%)	10 (38.4%)	P<0.05
Mild	12 (40%)	3 (30%)	Ns
Moderate	15 (50%)	6 (60%)	Ns
Severe	3 (10%)	1 (10%)	Ns
Aphthosis and halithosis	13 (23.6%)	4 (15.3%)	Ns
Mild	7 (53.8%)	4 (100%)	Ns
Moderate	4 (30.8%)	0	Ns
Severe	2 (15.4%)	0	Ns
Mucositis	11 (20%)	2 (7.6%)	Ns
Mild	8 (72.7%)	2 (100%)	Ns
Moderate	2 (18.2%)	0	Ns
Severe	1 (9.1%)	0	Ns
Mucorrhea	9 (16.3%)	8 (30.7%)	Ns
Mild	0	0	Ns
Moderate	6 (66.6%)	5 (62.5%)	Ns
Severe	3 (33.4%)	3 (37.5%)	Ns
Colitis	17 (30.9%)	8 (30.7%)	Ns
Mild	6 (35.3%)	5 (62.5%)	Ns
Moderate	8 (47%)	1 (12.5%)	Ns
Severe	3 (17.7%)	2 (25%)	Ns
Fatigue	24 (43.6%)	14 (53.8%)	Ns
Mild	5 (20.8%)	8 (57.2%)	P<0.05
Moderate	12 (50%)	3 (21.4%)	Ns
Severe	7 (29.2%)	3 (21.4%)	Ns
Hydroelectric alterations	8 (14.5%)	4 (15.3%)	Ns
Mild	6 (75%)	3 (75%)	Ns
Moderate	2 (25%)	1 (25%)	Ns
Severe	0	0	Ns
Diarrhea	25 (45.4%)	9 (34.6%)	Ns
Mild	9 (36%)	6 (66.7%)	Ns
Moderate	13 (52%)	3 (33.3%)	Ns
Severe	3 (12%)	0	Ns
Abdominal pain	20 (36.3%)	9 (34.6%)	Ns
Mild	8 (40%)	5 (55.5%)	Ns
Moderate	9 (45%)	1 (11.2%)	Ns
Severe	3 (15%)	3 (33.3%)	Ns
Constipation	12 (21.8%)	7 (26.9%)	Ns
Mild	5 (41.7%)	6 (85.7%)	Ns
Moderate	7 (58.3%)	1 (14.3%)	Ns
Severe	0	0	Ns
Moderate	0	0	Ns
Severe	1 (10%)	0	Ns
Dyschromia	12 (21.8%)	2 (7.6%)	Ns
Mild	7 (58.3%)	2 (100%)	Ns
Moderate	3 (25%)	0	Ns
Severe	2 (16.7%)	0	Ns
Alteration skin annex	6 (10.9%)	3 (11.5%)	Ns
Mild	5 (83.4%)	3 (100%)	Ns
Moderate	1 (16.6%)	0	Ns
Severe	0	0	Ns

halitosis, fatigue, hydroelectric alterations, dehydration, cutaneous dyschromia and cutaneous alterations) do not show any statistically significant difference after the 30 days of probiotic administration. Two groups of patients in two other cancer groups (breast and colon cancer) did not show any statistically significant results. However, most lung cancer symptoms (except for burning epigastric pain and mucositis) registered a reduction from T0 to T1. In the breast cancer group, in addition to the two previously mentioned symptoms, the overall occurrence of mucorrhea, fatigue, constipation, dyscromia and alteration of skin annexe did not improve after assuming the probiotic combination for 30 days.

From a clinical perspective, the absence of statistically significant differences must be interpreted with caution. The non significant outcome might be easily connected with the small sample, representing a clear limitation of this study and is expected to influence statistical results.

We can presume that the patients' health might not be extremely compromised by the anti-cancer therapy, since they are in an early stage of the treatment; this aspect is important as late administration of the probiotic might not be effective in a compromised health status (affected either by the progression of cancer and/or several cycles of anti-cancer therapies).

Our study's higher number of individuals diagnosed with prostate cancer might not be the only factor influencing statistically significant differences after using the probiotic combination. Prostate cancer was often treated with radiotherapy (55.4%) compared to the other types of cancer (breast: 10.6% and colon 5.4%) considered in this study. Despite the continuous effort to reduce or limit radiotherapy treatment side effects for cancer patients, heavy gastrointestinal disorders such as nausea and vomiting, flatulence, abdominal discomfort, and diarrhea are frequent (16,28).

The high number of patients who decided to withdraw their study participation might have negatively affected our results. The constant drop-out over time (from T0 to T1) could have implications for the statistical significance of the differences, especially in numerically smaller groups (breast and lung cancer). From the initial 38 individuals (T0) in the breast cancer group, only 16 were still engaged after the study (T1). In the lung cancer group, the patients at the beginning of the study were 22 (T0), but only 7 reached the end of the study (T1). Therefore, non-significant differences might have been caused by a low number of patients included in this study.

Despite the encouraging clinical results confirming the role of probiotics in contrasting diverse side-effects of anti-cancer therapies will require further studies with a higher number of patients and the application of more strict and well-defined parameters.

In conclusion, the current study laid out the premise for considering probiotics as add-on therapies in Oncology to improve the overall condition of patients.

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