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Probiotic bacteria in cancer patients undergoing chemotherapy and radiation therapy

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Probiotics;
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Summary
Background: Probiotics are live microorganisms, which as drugs or food supplements help to maintain health beneficial microbial balance in the digestive tract of a human or other host. Probiotics by their properties may help strengthen homeostasis and thus reduce side effects associated with cancer treatment. Experimental evidence suggests that probiotics might have beneficial effect on the toxicity of anticancer therapy.
Methods: A computer-based literature search was carried out using PubMed (keywords: ''probiotic'' and ''lactic acid bacteria'' in association with the search terms ''cancer'' or ,,oncology'' or ''chemotherapy'' or ''radiation''); data reported at international meetings were included.
Results: Probiotics might have beneficial effects on some aspects of toxicity related to anticancer treatment especially radiation therapy. However, reported trials vary in utilized probiotic strains, dose of probiotics and vast majority of them are small trials with substantial risk of bias. Despite limited data, it seems that probiotic bacteria as live microorganisms could be safely administered even in the setting of neutropenia.
Conclusions: Current evidence supporting probiotic use as adjunctive therapy to anticancer treatment is limited, especially in cancer patients treated with chemotherapy. Well designed clinical trials are needed to find true role of probiotics in oncology.

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Introduction

It is supposed, that complementary and alternative medicine, like vitamins, minerals, herbs and other dietary supplements including probiotics, is used by more than 80% of cancer patients.[1] Probiotics are live microorganisms, which as drugs or food supplements help to maintain health beneficial microbial balance in the digestive tract of a human or other host.[2] There is rising interest in probiotics, which is also reflected in a number of published works in this area. They are tested in multiple indications including gastrointestinal disorders like prevention and treatment of infectious and antibiotic-induced diarrhea, treatment of liver insufficiency, lactose intolerance, inflammatory bowel disease, irritable bowel syndrome. Probiotics are also evaluated in rheumatic and allergic diseases, in the prevention of urogenital infections or in cardiology based on their effect on serum cholesterol, lipids or hypertension.[3–5]

The concept of probiotics was raised first time in the early of 20th century by Elie Metchnikoff, Russian Nobel laureate, who discovered that some strains of bacteria present in human bodies were beneficial to various human processes. These good bacteria were named probiotics. It is supposed that beneficial effects of probiotic bacteria are associated mainly with their impact on composition of intestinal microflora and by stimulation of the immune system.[6] Most probiotics belong to a group of lactic-acid producing bacteria (lactobacilli, streptococci, and bifidobacteria). Some are nonhuman strains used in the fermentation of dairy products, while, others are derived from the intestinal microbiota of healthy humans. Species from other bacterial genera such as *Streptococcus*, *Bacillus*, and *Enterococcus* have also been used as probiotics, however, there are concerns regarding the safety of such probiotics because these genera contain many pathogenic species, especially *Enterococcus*. Nonbacterial microorganisms such as yeasts from the genus *Saccharomyces* have also been used as probiotics for many years.[6] Compared to pathogenic bacteria, probiotics are generally considered as safe and infections caused by probiotics are extremely rare in healthy persons. Probiotic bacteria are non-invasive despite strong adherence to intestinal epithelium and they should be non-pathogenic. Usually, they colonize human intestine only transiently and they don't produce toxins and/or metabolites dangerous for human health.[6]

In oncology, main interest in probiotics is in the area of cancer prevention, especially of colorectal cancer.[7] However, there is rationale to use probiotics as an adjunctive therapy to anticancer treatment, but current evidence is still limited mainly because of the risk of inducing iatrogenic infection and lack of robust efficacy data. Cancer patients are immunocompromised due to cancer as well as due to anticancer treatment. On the other hand, due to the frequent use of chemotherapy, radiation therapy and especially antibiotics, there is a breach of natural protective barriers to colonization by pathogenic microorganisms and the emergence of multiresistant strains. Probiotics by their properties may help strengthen homeostasis and thus reduce side effects associated with cancer treatment. Experimental and some clinical evidence suggest that lactic acid bacteria might have beneficial effect on the toxicity of anticancer therapy.[8–10]

Probiotics are relatively cheap and are easily available for cancer patients without prescription restriction. It is supposed that many cancer patients use probiotics during course of their disease, but exact epidemiological data are lacking. Probiotics are live organisms and there is still limited evidence for their effectivity and safety in cancer patients treated with chemotherapy or radiation therapy.

In this review, we present current evidence of the status of probiotics in clinical oncology, their potential clinical position as a part of anticancer treatment, and safety concerns associated with their application.

Probiotics and chemotherapy

Chemotherapy is a mainstay in the anticancer treatment. However, it is associated with some toxicity in vast majority of patients. These include hematological toxicity, gastrointestinal toxicity, alopecia, organ toxicity as well as constitutional toxicity like chemotherapy related fatigue.

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One of the most serious manifestations of hematological toxicity is neutropenia with the subsequent risk of infectious complications due to immunosupression.[11–12] The risk of infection increased with duration and severity of neutropenia. Gastrointestinal toxicity is mainly related to mucosal damage by chemotherapy, decreased colonization resistance and alteration of natural host microflora. It has been estimated that within 1 day of admission to the hospital, approximately one half of the endogenous flora of gut of neutropenic patients becomes altered, with aerobic Gram-negative (often nosocomial) strains replacing the usual flora.[13] Probiotics by their properties may decrease the risk and severity of chemotherapy related toxicity and thus reduce side effects associated with cancer treatment. Probiotics were evaluated mainly in prevention of infectious complications of chemotherapy and chemotherapy related diarrhea.

Prevention of infections and febrile neutropenia in patients undergoing chemotherapy

Infections in cancer patients are often preceded by bowel colonization with pathogenic bacteria followed by translocation across the gut mucosa and systemic dissemination.[14,15] Alteration in bowel flora is the result of chemotherapy and particularly of the use of broad-spectrum antibiotics suppressing the growths of normal anaerobic bowel flora leading to diminishing of colonization resistance. Maintenance of the natural commensal flora provides a potent barrier to acquisition of pathogenic aerobic Gram-negative rods.[16] Approximately 80% of infection in neutropenics are caused by endogenous flora and the main entrance is intestinal mucosa.[14] Microflora of large intestine consists of approximately 500 bacterial species, and their concentration reaches up to 10^{11} cell per gram of luminal content.[17] The microflora represents an important barrier against pathogens and produces short chain fatty acids that are the main source of nutrition for colonocytes.[6] Resident bacteria are crucial in defence against colonization by exogenous microbes and in prevention of pathogens invasion to tissues. Prevention of febrile neutropenia by selective decontamination of bowel by quinolones and trimethoprim–sulfamethoxazole was only partially successful leading to development of multiresistant strains. In addition, this treatment does not affect the incidence of Gram-positive infections and is expensive.[18] For the reduction of frequency of gut colonization by virulent bacteria, the germ free environment was considered to be an important tool for reduction of infections in neutropenic patients. In one trial researchers compared protective isolation with standard hospital care in neutropenic patients with acute leukemia.[19] The two groups were similar with respect to incidence of infection and fever. Paradoxically, the rate of bacteremia was higher in patients randomized to protective isolation.

Competitive inhibition of bowel colonization by pathogenic microorganisms by probiotics might be a useful prevention of infections in cancer patients.[10] In comparison with the existing selective bowel decontamination by quinolones and/or trimethoprim–sulfamethoxazole, we can expect a decreased incidence of mycotic and Gram-positive infections based on the effect of bowel microflora. Beneficial effects of probiotic bacteria consists of increased transepithelial resistance by stimulation of the immune system with subsequent reduced time of neutropenia, competition for nutrition with pathogenic bacteria, competitive inhibition of bacterial adhesion sites and in the production of bacteriocins.[16,20–23] Lactic acid bacteria could be involved in the treatment dysmicrobia after antibiotics and their enzymatic activity affects the activation or deactivation of metabolites inducing diarrhea. Lactic acid bacteria during fermentation produce short-chain fatty acids, including butyric acid, and thus, they provide nutrition for colonocytes and participate in the restitution of colonocytes after chemotherapy.[10,11] Therefore, augmentation of colonization resistance by lactic acid bacteria might be effective and inexpensive way for infection prevention in granulocytopenic patients. This hypothesis was tested in animal models and small clinical trials.[9,24]

Preclinical trials

In experimental models, it was shown, that germ-free animals have higher rates of infection and are more susceptible to infection in comparison to normal animals.[25,26] In animal model, in cyclophosphamide-induced neutropenia administration of heat inactivated strain *Enterococcus faecalis* FK-23 led to shortening of duration of neutropenia and to augmentation of leukocyte reconstituting capacity.[24] Also oral or intraperitoneal prophylactic administration of FK-23 preparation to mice significantly prolonged survival periods of mice infected by *Candida albicans*, and decreased viable counts of *C. albicans* recovered from their kidneys.[27]

Clinical trials

There are only anecdotal reports in the literature concerning the use of probiotics in granulocytopenic patients. In a small study, Hengens and Klastersky administered a strain of lactobacilli to five granulocytopenic patients with intestinal flora suppressed by antibiotics (Table 1). Lactobacilli were not successful in spontaneous recolonization of bowel by enteric bacteria. However, in only two patients significant number of lactobacilli in stool was detected.[28] In randomized study 33 children with leukemia and solid tumors received framycetin, colimycin, nystatin, and metronidazole in 35 neutropenic episodes, while 35 children received co-trimoxazole with lactobacilli in 35 episodes. There were neither significant differences in incidence of infections during neutropenia nor in duration of neutropenia. Combination of co-trimoxazole with lactobacilli was considerably better tolerated.[29] The problem of these studies is the limited number of participants and the dose of the probiotic itself. For colonization resistance only massive doses of the probiotic must be used.

Efficacy and safety of the probiotic strain *Enterococcus faecium* M74 in neutropenic patients with solid and hematological malignancies was evaluated in two small studies.[9,10] In phase I study, the probiotics were administered to six patients with testicular cancer treated with chemotherapy. The febrile episode was not observed in any of the patients.

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Table 1 Indication, strain of probiotic and amount of applicated probiotics in clinical trials in cancer patients undergoing chemotherapy and radiation therapy.

Indication	Tumor type	Probiotic strain	Probiotic dose	Result of evaluation/evidence	Reference no.
Prevention of infection in patients treated with chemotherapy	Leukemia and solid tumors	*Lactobacillus* sp.	Not reported	no effect	28
Prevention of febrile neutropenia	Leukemia and solid tumors	*Lactobacillus* sp.	Not reported	no effect	29
Prevention of febrile neutropenia	Testicular cancer, Acute leukemia	*Enterococcus faecium* M-74	$6-18 \times 10^9$ per day	no effect	9
Prevention of febrile neutropenia	Leukemia	*Enterococcus faecium* M-74	36×10^9 per day	no effect	10
Prevention of infection in patients treated with chemotherapy	Various pediatric malignancies	*Bifidobacterium breve* strain Yakult,	At least 1×10^9 per day	weak positive	30
Prevention of gastrointestinal toxicity of 5-Fluorouracil chemotherapy	Colorectal cancer	*Lactobacillus rhamnosus* GG	$1-2 \times 10^{10}$ per day	strong positive	46
Prevention of intestinal side-effects of radiotherapy	Cervical and uterine cancer	*Lactobacillus acidophilus*	At least 2×10^{10} per day	strong positive	58
Prevention of radiation-induced diarrhea	Cervical, sigmoid or rectal cancer treated with postoperative radiation therapy	VSL no. 3	450×10^9 CFU/g three times per day	strong positive	59
Prevention of radiation-induced diarrhea	Cervical cancer and endometrial cancer	*Lactobacillus casei* DN-114 001	10^8 CFU/g three times per day	no effect	60
Treatment of radiation-induced diarrhea	Mixture of cancer in lower abdomen treated with postoperative radiotherapy	*Lactobacillus rhamnosus*	1.5×10^9 CFU three times per day	weak positive	62
Prevention of radiation induced mucosities	Head and neck cancer treated with chemo-radiotherapy	*Lactobacillus brevis* CD2 *lozenges*	At least 2×10^9 six time per day	strong positive	63

Abbreviations: CFU—colony forming unit.

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Then *E. faecium* M-74 was administered to five patients with relapsed acute leukemia. During 127 days of severe neutropenia, 12 febrile episodes occurred. No febrile episode or infection provoked by the tested strain was noted.[9]

Subsequently an open-label, nonrandomized, phase II study was performed.[10] The primary end point of the study was the prevention of febrile neutropenia by probiotic strain *E. faecium* M-74 during the induction and consolidation chemotherapy in patients with acute and chronic myelogenous leukemia. Fourteen patients were included in the study. Patients received prophylaxis with *E. faecium* M-74 during one cycle of chemotherapy. The daily dose was 36×10^9 CFU (colony forming units) tid. All patients experienced febrile neutropenia. During 231 days of severe neutropenia, 30 febrile episodes occurred, but none of them was provoked by the study strain. The administration of this bacterial strain was not effective in the prevention of febrile neutropenia, but this does not preclude the protective effect of other probiotic strains. Moreover, tolerance of therapy was excellent without significant adverse effects in both studies.[10]

Based on this experience, double-blinded, randomized, multicentric, placebo controlled phase III study was designed, aimed to reduce incidence of febrile neutropenia and gastrointestinal complication in children after chemotherapy by synbiotic preparation. Patients in active group receive mixture of two probiotic strains (*Lactobacillus rhamnosus* LGG and *Bifidobacterium animalis* subspec. *lactis*, BB-12) together with oligofructose-enriched inulin. Final data are awaited by the end of 2014.

Another similar randomized placebo-controlled trial was performed to evaluate the effects of the enteral administration of the probiotic, *Bifidobacterium breve* strain Yakult, on its ability to prevent infection, fecal micro flora, and intestinal environments in cancer patients receiving chemotherapy ($n = 42$).[30] The study product contained 10^9 freeze-dried, living BBG-01, cornstarch, and hydroxypropyl cellulose. Administration of this preparation led to lower frequency of fever and use of intravenous antibiotics in the active group. The probiotic administration also enhanced the habitation of anaerobes, while increased levels of *Enterobacteriaceae*, one of the facultative anaerobes, were observed at more pronounced manner in the placebo group.[30] The concentration of organic acids produced by anaerobes maintains the intestinal acidity and inhibits the colonization of pathogenic organisms.[31,32] In this study the concentrations of total organic acids were maintained most of the time at the normal level, which constantly maintained the pH below 7.0 only in the probiotic group.[30]

Prevention and treatment of chemotherapy related diarrhea by probiotics

Diarrhea is a common complication of chemotherapy. Several mechanisms play role in the development of chemotherapy related diarrhea including malabsorption due to mucositis induced by chemotherapy, dysmicrobia induced by broad-spectrum antibiotics and predisposition to infectious diarrhea in immunocompromised patients. Some cytostatics and their metabolites induce diarrhea through direct effects on the intestinal mucosa.[33]

Preclinical trials

Some animal studies investigated role of probiotics in the prevention of chemotherapy induced diarrhea. VSL 3 probiotic formula was effective in preventing of irinotecan induced diarrhea in rat model of chemotherapy induced diarrhea.[34] Another study suggests beneficial effect of *Streptococcus thermophilus* TH-4 on intestinal mucositis induced by the chemotherapeutic agent, 5-fluorouracil (5-FU).[35] These data support rationale to use probiotics in chemotherapy induced diarrhea, however, clinical data are still limited.

Clinical trials

Cancer patients treated with chemotherapy are often exposed to antibiotic treatment during treatment of febrile neutropenia or other infections associated with cancer induced immunosupression.[36] Effects of probiotics on antibiotic-induced diarrhea is well established. Several single trials as well as meta-analysis support the beneficial role of lactic acid bacteria in this setting, including immunocompromised patients.[37–39] Meta-analyses confirmed efficacy of probiotics in prevention of antibiotic induced diarrhea including *Clostridium difficile* infection in adults [38–40] and suggest their beneficial role in children, especially when higher doses of probiotics are administered.[41,42]

Several group of cancer patients had higher incidence of diarrhea. This includes patients with hematological malignancies with prolonged neutropenia after chemotherapy, or patients treated with anticancer drugs with direct diarrhea inducing effects. There is limited experience with probiotics in the prevention and treatment of diarrhea related to chemotherapy, however, several trials are ongoing (Table 2). The incidence of diarrhea during treatment of acute leukemia is between 15% and 80%.[43,44] Severe diarrhea grade 3—4 is in the 8—20% and is more common during the induction phase of chemotherapy. In a phase II trial preventive administration of probiotic strain *E. faecium* M-74 with selenium was associated with a low incidence (14%) and severity (all grade 1) diarrhea, despite the fact that half of the patients received induction therapy.[10]

Irinotecan is one of key drug used in the treatment of colorectal cancer. The incidence of irinotecan induced diarrhea varies between 60 and 90%, with severe diarrhea occurring in 20—40% of patients receiving irinotecan.[33] The main cause of diarrhea is one of irinotecan metabolites, SN-38 which is in the liver glucuronidated and subsequently expelled into the intestine. Due to the bacterial enzyme beta-D-glucuronidase in intestinal lumen it is deconjugated. This form causes direct damage of intestinal mucosa associated with malabsorption and the development of diarrhea.[33] Irinotecan induced diarrhea is usually treated with loperamid by decreasing the activity of the myenteric plexus, but dose reduction of irinotecan is often necessary. It is known that probiotic bacteria, reduce activity of intestinal beta-D-glucuronidase and therefore these bacteria could be applied in the prevention of diarrhea in patients treated by this food supplement. Given their low toxicity, good tolerability, probiotics may be an important part of supportive therapy. Recently, we initiated phase III trial aimed to determine the preventive effect of probiotics on irinotecan

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Table 2 Selected ongoing trials investigating probiotics in clinical oncology.

Trial number*	Objectives	Patient population	Intervention	Stage of trial	Country
NCT01644097	Prevention of chemotherapy related diarrhea	Cancer patients treated by chemotherapy	Mixture of *Lactobacillus plantarum* strain 299v, *Bifidobacterium lactis* and *Lactobacillus acidophilus*	Phase II	USA
NCT01473290	Prevention of gastrointestinal complication	Cancer patients treated by chemotherapy or radiation therapy to pelvic region	VSL no. 3 (mixture of probiotic strains)	Phase III	USA
NCT01723592	Improvement the quality of the vaginal flora	Women with breast cancer treated with chemotherapy	Mixture of probiotic strains of *L. rhamnosus*, *L. jensenii*, *L. crispatus*, *L. gasseri*	Phase II	Austria
NCT00197873	Prevention of chemotherapy related diarrhea	Patients on 1st line CAPOX treatment for metastatic colorectal cancer	*L. rhamnosus* GG	Phase II	Finland
NCT01579591	Pathological major response rate in patients with rectal cancer	Rectal cancer patients undergoing concurrent chemotherapy and radiation therapy	VSL no. 3 (mixture of probiotic strains)	Phase III	Italy
NCT01410955	Prevention of irinotecan induced diarrhea	Metastatic colorectal cancer patients treated with irinotecan based chemotherapy	Colon Dophilus™ (mixture of probiotic strains and inulin)	Phase III	Slovakia
NCT01480011	Prevention of high-dose chemotherapy induced oral mucosities	Cancer patients treated with high dose chemotherapy with autologous stem cell transplantation	*Lactobacillus* CD2 Lozenges	Phase II	India
NCT01706393	Prevention of radiation induced enteropathy	Cancer patients treated with abdominal/pelvic radiation therapy	(mixture of several probiotic strains)	Phase II	South Korea

* ClinicalTrials.gov identifier.
Abbreviation: CAPOX (capecitabine and oxaliplatin)

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associated diarrhea. Final results of this study are awaited by the end of 2013 (Table 2).

Administration of 5-fluorouracil (5-FU), one of the key anticancer drugs in treatment of colorectal cancer is associated not only with direct mucosal damage, but is associated with development of lactose intolerance and diarrhea as well. Its incidence increases with duration of administration of 5-fluorouracil. Administration of probiotics might alleviate diarrhea in a similar manner like in general population with lactose intolerance.[45]

In a clinical study patients diagnosed with colorectal cancer ($n = 150$) were randomly allocated to receive monthly 5-FU and leucovorin bolus injections or a bimonthly 5-FU bolus plus continuous infusion for 24 weeks as postoperative adjuvant therapy. On the basis of random allocation, the study participants did or did not receive *L. rhamnosus* GG supplementation ($1-2 \times 10^{10}$ per day) and fibre (11 g guar gum per day) during chemotherapy. Patients who received Lactobacillus had less grade 3 or 4 diarrhea (22 vs. 37%, $p = 0.027$), reported less abdominal discomfort, needed less hospital care and had fewer chemotherapy dose reductions due to bowel toxicity. No Lactobacillus-related toxicity was detected. Guar gum supplementation had no influence on chemotherapy tolerability.[46]

Probiotics and radiation therapy

Radiation therapy is inherent part of anticancer treatment; however, it is associated with several adverse effects. Some of them are related to mucosal damage by ionizing radiation, with subsequent alteration of intestinal flora, accelerated small and large bowel transit, malabsorption of bile salts and development of gastrointestinal toxicity manifested in the form of diarrhea, nausea or loss of appetite.[47,48]. Diarrhea is the most significant toxicity of patients undergoing radiation therapy to the area of the abdomen and pelvis. The incidence of diarrhea ranges from 50 to 90% when total tumoricidal dose of 45 Gy is administered.[49] It could be treated with antidiarrheal drugs like loperamid, but in severe cases, radiation therapy interruption and/or parenteral nutrition support is necessary. While chemotherapy is mostly associated with the development of neutropenia, administration of radiotherapy alone usually is not associated with severe hematological toxicity and therefore the risk of iatrogenic infection caused by probiotics is very low. This is a reason, with relatively more experience with probiotics in patients treated with radiation therapy.

Preclinical trials

Experimental animal models have shown that intestinal microbiota plays a role in the development of radiation-induced intestinal damage, because it was shown, that germ-free animals are more resistant to lethal radiation enteritis.[50] Radiation reduces the intestinal motility[51,52] and consecutive slower stool transit can lead to bacterial overgrowth, especially from Gram-negative bacteria,[51] described in up to 45% of patients with post-radiation diarrhea.[53] This imbalance together with inflammatory response could increase the permeability of the mucosa barrier and promote the bacterial translocation,[54] which can subsequently lead to development of pelvic sepsis described in 3% to 4% of patients during treatment.[47,49]

Two animal studies investigated the effect of probiotic supplementation in irradiated male Wistar rats. The first study supported the potential of *Lactobacillus delbrueckii*, subspec. *Bulgaricus* B3 strain, in the prevention of post-radiation intestinal damage as well as in prevention of gastrointestinal toxicity.[55] In the other study animals received probiotic mixture containing *Lactobacillus acidophilus*, *Lactobacillus helveticus* and *Bifidobacterium* sp. to evaluate bacterial translocation and endotoxinemia after abdominal irradiation. Rats receiving probiotic supplementation presented a statistically significant reduction of endotoxin levels and bacterial translocation. Probiotics administration was associated with qualitative change in bacterial translocation. Gram-negative bacteria were predominant in blood cultures of rats fed with placebo, while Gram-positive bacteria were more common in blood samples from probiotic group.[56] Recent animal study showed, that probiotic protects intestinal epithelium from radiation injury in a TLR-2/cyclo-oxygenase-2-dependent manner.[57]

Clinical trials

Several, randomized clinical trials and one meta-analysis examined preventive and therapeutic role of probiotics in patients treated with radiation therapy and some are ongoing, (Tables 1–3). Three trials focused on prevention of radiation related diarrhea.[58–60]

The pilot controlled trial included only 21 patients with cervical or uterine carcinoma treated with radiotherapy. This trial showed beneficial effect of probiotics in this patients' population, however, this study had several weaknesses including a small sample size and lack of double-blinded placebo-controlled design.[58]

Large trial, investigated the efficacy of probiotic *Lactobacillus case*i DN-114 001 to reduce the incidence of radiation-induced diarrhea in patients with advanced cervical and/or endometrial carcinoma undergoing pelvic radiotherapy or chemoradiotherapy. In this trial 115 patients were randomized, but only 85 patients were included to final analysis. This trial was double blind; placebo controlled study, and it didn't show statistically significant differences between two randomized arms. This study had some limitations as well, including insufficient statistical power, relatively low dose of utilized probiotic strain, and heterogeneity of treatment populations, when some patients undergo only radiation while some we treated with concomitant chemo-radiotherapy.[60]

The largest of these trials included 482 patients. This was a double-blinded, randomized, placebo-controlled study. The study investigate probiotic formula VS 3, containing viable lyophilized bacteria from several different strains of lactobacilli (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbruekii* subsp. *bulgaricus*), bifidobacteria (*B. longum*, *B. breve*, *B. infantis*) and 1 strain of *Streptococcus salivarius* subsp. *thermophilus*. This study conclusively confirmed that VSL 3 is an effective and safe preventive therapy. Patients receiving probiotics had significantly lower incidence (31.6%

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Table 3 Clinical trials evaluating preventive and therapeutic role of probiotics in patients treated with radiation therapy.

Author	Randomized patients (patients in analysis)	Study aim	Patient population	Study arms	Study outcome
Salminen[58]	24 (21)	Prevention	Cervical and uterine cancer treated with radiotherapy	*Lactobacillus acidophilus* vs. no intervention	Diarrhea probiotics: 27% control: 90% $p < 0.05$ Rescue medication for diarrhea probiotics: 9% control: 60% $p < 0.05$
Urbancsek[62]	205 (205)	Treatment	Mixture of cancer in lower abdomen treated with postoperative radiotherapy	*Lactobacillus rhamnosus* vs. placebo	Need for rescue medication for diarrhea probiotics: 35% placebo: 48% $p = NS$
Delia[59]	490 (482)	Prevention	Cervical, sigmoid or rectal cancer treated with postoperative radiation therapy	VSL no. 3 (mixture of probiotic strains) vs. placebo	Diarrhea (all grades) probiotics: 31.6% placebo: 51.8% $p < 0.001$
Giralt[60]	118 (85)	Prevention	Cervical cancer treated with chemo-radiation therapy or endometrial cancer treated with radiotherapy	*Lactobacillus casei* DN-114 001 vs. placebo	Co-primary endpoint defined as: at least 4 or more bowel movements, need for rescue medication, or premature withdrawal because of lack of efficacy. probiotics: 68.2% placebo: 58.5% $p = NS$
Sharma[63]	200 (188)	Prevention	Head and neck cancer treated with chemo-radiotherapy	*Lactobacillus brevis* CD2 *lozenges* vs. placebo	Grade III and IV mucositis: probiotics: 52% placebo: 77% $p < 0.001$ Anticancer treatment completion rates: probiotics: 92% placebo: 70% $p = 0.001$

Abbreviations: NS—non-significant.

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vs. 51.8%, $p < 0.001$) and also severity of diarrhea compared to placebo. Authors also reported significantly lower mean daily number of bowel movements and shorter time of rescue medication use (loperamide) in probiotic group.[59]

Meta-analysis of these 3 preventive trials included 632 patients and it did not show significant benefit of probiotics compared to placebo in prevention of radiation-induced diarrhea (odds ratio = 0.47; 95% confidence interval: 0.13—1.67). However, few available trials and the presence of significant clinical and statistical heterogeneity limited the analysis.[8] No major adverse events owing to probiotic supplementation were reported in any study. However, few available clinical studies do not allow firm conclusions.[8] In addition to these mentioned results one case study suggested that probiotics can be used effectively in the management of chemotherapy-induced diarrhea in patients with advanced breast cancer.[61]

Only one clinical trial evaluated probiotic supplementation as a treatment for acute radiation-induced diarrhea.[62] This randomized, placebo-controlled, double-blinded trial investigated the treatment efficacy of 1-week supplementation with *L. rhamnosus* based on the need of rescue medication per patient. This study included 202 patients. Authors observed trend for beneficial effect of probiotics compared to placebo in the treatment of radiation-related diarrhea; however, the differences didn't reach statistical significance. Patients' rating of diarrhea and feces consistency was in favor of probiotic supplementation.[62]

Oral mucositis is a frequent and serious complication in patients receiving chemo-radiotherapy for head and neck cancer. Recently published study evaluated the effects of administering *Lactobacillus brevis* CD2 lozenges on the incidence and severity of mucositis and tolerance to chemo-radiotherapy.[63] This randomized, double-blind study included 200 patients, who were treated with chemoradiation. The efficacy analysis included the 188 patients who received $\geq$1 week of study treatment. This study showed beneficial effect of probiotic supplementation on primary endpoints (Table 3). Moreover, a larger proportion of patients remained free of mucositis when treated with *L. brevis* CD2 compared to the placebo (28% vs. 7%). This study suggest that beneficial role of probiotics in prevention of radiation induced toxicity is not restricted to prevention of diarrhea.[63]

Safety

Probiotics fall into the category of organisms classified as ''generally regarded as safe''- GRAS.[64] The safety concerns with probiotic administration in cancer patients are related mainly to risk of infection caused by probiotic bacteria and transfer of antibiotics resistance.

Many probiotics strains are naturally resistant to antibiotics, but majority of this resistance is intrinsic (chromosomally encoded) and therefore nontransmissible.[65—68] This could be a danger, when probiotics become infectious agents, on the other hand probiotic strains with intrinsically antibiotic-resistance may benefit patients, whose normal intestinal microflora has become greatly reduced or unbalanced due to the administration of various antimicrobial agents.[69] For some strains (e.g. *Lactobacillus* GG) the plasmid-free status was proven,[70] but at the same time it was shown, that some strains may carry potentially transmissible plasmid-encoded antibiotic resistance genes.[71—75] There exists a possible risk with respect to the development and transfer of antibiotic resistance between probiotic strain and endogenous flora, which could lead to the formation of new antibiotic-resistant pathogens.[69,76—79] Therefore, one of the key requirement for probiotic strains is that they should not carry transmissible antibiotic resistance genes.[69,76,77]

Despite the fact, that the incidence of infection caused by lactic acid bacteria is extremely low, there exists certain risk, that they become pathogenic.[80] This risk naturally increases in immunocompromised patients. Therefore, this is one of the main reasons for limited experience with administration of probiotics in granulocytopenic patients. In addition, due to chemotherapy it comes not only to neutropenia but also to local affection of gut mucosa. Another mechanism is bacterial translocation. It was defined as the passage of viable indigenous bacteria from the gastrointestinal tract to extraintestinal sites[81] and may result in the transfer of bacteria to other organs, thereby potentially causing bacteremia, septicemia, and multiple organ failure.[82]

In case reports lactic acid bacteria are mentioned as causing local infections such as chest infections, digestive tract infections, urinary tract infections, and meningitis.[80,83] *Lactobacillus* sp. is probably most common probiotic species associated to bacteremia, but which has a very low mortality rate.[84] *Bacillus subtillis* bacteremia occurred in 4 of 20 oncologic patients, but was also reported in other severely sick patients.[85] The experience of our hospital confirms this fact, too. Fungemia caused by *Saccharomyces* was also reported in a neutropenic patient with acute leukemia. It was a 6 months-old child that received diarrhea prophylaxis by *Saccharomyces boulardii*.[86] A similar infection was also noted in two other immunocompromised persons receiving the prophylaxis by *S. boulardii*.[87]

Systematic review identified 11,977 publications, of which 622 studies were included in the review.[88] Across all included studies and treatment arms, 24,615 participants used a probiotic product.[88] Based on reported adverse events, randomized controlled trials showed no statistically significantly increased relative risk (RR) of the overall number of experienced adverse events (RR = 1.00; 95%CI: 0.93, 1.07, $p = 0.999$); gastrointestinal; infections; or other adverse events, including serious adverse events (RR = 1.06; 95%CI: 0.97, 1.16; $p = 0.201$), associated with short-term probiotic use compared to control group participants; long-term effects are largely unknown. Case studies suggested that participants with compromised health are most likely to experience adverse events associated with probiotics. However, RCTs in medium-risk and critically ill participants did not report a statistically significantly increased risk of adverse events compared to control group participants.[88] In conclusion authors of this analysis state, that the available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence.[88]

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Conclusions and future directions

In conclusion, current evidence supporting probiotic use as adjunctive therapy to anticancer treatment is limited, especially in cancer patients treated with chemotherapy. The reported trials vary in utilized probiotic strains, dose of probiotics and vast majority of them are small trials with substantial risk of bias. Some of the reports support their beneficial effects on certain aspects of toxicity related to chemotherapy and radiation therapy; however, large, properly designed clinical trials are needed to assess their real position as a part of anticancer treatment. Despite limited data, it seems that probiotic bacteria as live microorganisms could be safely administered even in setting of neutropenia. Future research should focus on selection of most effective and safe probiotic strains and their combinations, and/or administration of probiotics with prebiotics to increase their success in maintaining colonization resistance and in prevention of the adverse events of anticancer treatment.

Conflict of interest statement

None declared.

Review criteria

Information for this Review was compiled by searching the PubMed and MEDLINE databases for articles published before 1 January 2013. Only articles published in English were considered. The search terms included ''probiotic'' and ''lactic acid bacteria'' in association with the search terms ''cancer'' or ''oncology'' or ''chemotherapy'' or ''radiation'' within the article title or abstract. Full articles were obtained and references were checked for additional material when appropriate.

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