Microbiota Modulation in Cancer Survivors

Subjects: Oncology

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Chemotherapy, targeting not only malignant but also healthy cells, causes many undesirable side effects in cancer patients. Interventions and supportive care for treatment-induced late effects remain an emerging area of research in long-term cancer survivors. Due to the lack of preventive measures and approved pharmacological agents, different possibilities in preventing or mitigating the late toxicities need to be assessed. Targeting the gut microbiome in cancer survivors might represent a new potential trend being in its infancy to date. Gut microbiota disruption after chemo- and radiotherapy can be recovered by several mechanisms including administration of probiotics and/or prebiotics and FMT. Interestingly, the relationship between diet, physical activity, and gut microbiome appears to be another potential tool in cancer survivors. However, most of the data dealing with neuro- and cardioprotective effects of microbiota modulation came from preclinical and non-cancer patients´ clinical studies, and further evaluations in cancer patients are highly warranted.

microbiome cancer survivors chemotherapy-induced side effects cognitive impairment cardiovascular toxicity microbiota modulation

1. Neuro- and Cardioprotective Effect of Probiotics

In cancer patients, the administration of probiotics is mainly aimed to alleviate the adverse effects of chemo- and radiotherapy and reduce gastrointestinal toxicity while increasing bacterial diversity. Interestingly, a survey study comprising 499 cancer patients documented a probiotic consumption in 28,5% of all participants [1]. Several studies focusing on the pre- and post-treatment probiotic supplementation reported improved immune responses and the reduction of infectious complications in patients with a different spectrum of malignancies [2] [3] [4]. Probiotic bacteria produce antimicrobials, compete with pathogens for nutrients, or adhere to intestinal epithelial cells, and physically block the adhesion of pathogens resulting in high colonization resistance [5].

A limited number of clinical trials concerning probiotic use to ameliorate the chemotherapy-related side effects on behavioral comorbidities or cognitive impairment have been conducted so far. Lee et al. showed that *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* were able to reduce the symptoms of depression, anxiety, and fatigue in colorectal cancer survivors [6]. Recently, a randomized double-blind and placebo-controlled trial comprising 120 elderly patients following elective orthopedic or colorectal cancer surgery found an association between the perioperative application of oral probiotics and postoperative reduction in cognitive impairment. In addition, increased microbiota diversity and decrease plasma IL-6 and cortisol levels were observed in the group of probiotic patients suggesting a possible mechanism via reducing the peripheral inflammation, and the stress response [7]. Interestingly, the probiotic intervention was found to reduce the clinical anxiety before surgery by the suppression

of serum corticotropin-releasing factor levels and avoiding the increase in heartbeat among patients with laryngeal cancer [8].

Neuroprotective effects of probiotics have been detected in numerous experimental models and clinical trials dealing with behavioral dysfunctions and neurodegenerative disorders. Probiotic metabolites such as SCFA play a role in maintaining the BBB integrity through the increased expression of claudin and occludin in the membrane. Moreover, the production of tryptophan metabolites might block proinflammatory NFk-B, VEGF-B, and the activation of astrocytes, and microglial cells within the brain [9]. According to the findings from mouse models, long-term probiotic administration reduced anxiety and depression, normalized the immune response, caused changes in GABA production, diminished oxidative stress markers in the brain, enhanced activities of antioxidant enzymes, preserved neuronal synaptic plasticity, and restored basal noradrenaline levels in the brainstem [10] [11] [12] [13]. A positive link between *Bifidobacterium longum* 1714 consumption and stress reduction as well as improved memory was indicated in a clinical study comprising male healthy participants [14]. Accordingly, another study on human volunteers showed beneficial effects of oral intake of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 on anxiety and depression-related behaviors [15]. In a recent meta-analysis of 19 double-blind, randomized, placebo-controlled trials, Goh et al. confirmed the beneficial effect of probiotics on depressive symptoms in patients with the major depressive disorder (MDD) [16].

Besides neuroprotective, cardioprotective effects of probiotics have also been reported. In particular, mouse and rat models demonstrated reduced cardiomyocyte apoptosis, a protective effect of myocardial damage, improved cardiac function, and survival in animals after exposure to *Lactobacillus* spp. [17] [18]. According to the findings, the administration of a probiotic *Lactobacillus rhamnosus* GR-1 has attenuated post-infarction remodeling and heart failure in rats subjected to sustained coronary artery ligation [19]. A cardioprotective effect against heart ischemic injury through the attenuation of TNF-α and oxidative stress was observed in a rat myocardial infarction model after receiving the combination of four viable probiotic bacteria strains *Bifidobacterium breve*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Lactobacillus acidophilus* [20]. Importantly, probiotic consumption in patients with heart failure has led to an improvement in disease-related parameters [21].

2. Fecal Microbiota Transplantation and Improvements in Neurologic Functions and Cancer Treatment Efficacy

FMT represents the transfer of intestinal microbiota from a healthy donor into the patient's intestine. Currently, FMT is predominantly used in the treatment of severe and life-threatening intestinal inflammation caused by *Clostridium* spp. where antibiotic treatment fails. Nevertheless, FMT modulation was associated with improvements in neurologic functions, possibly along the microbiota-gut-brain axis. In particular, reduction in cognitive deficits, a decrease of TNF-induced neuroinflammation, an increase in serotonin levels as well as improvement in motor skills in mouse models of Alzheimer's and Parkinson's disease were reported [22] [23]. Bercik et al. demonstrated the changes in brain chemistry and behavior after microbiota disruption in healthy mice. According to their results, adoptive transfer experiments with cecal bacteria reported altered exploratory behavior of GF mice after colonization with microbiota from different mouse strains [24]. Translational studies concerning the transplantation of

patients´ gut microbiota to GF or microbiota-deficient rodents documented alterations in several neurobehavioural features. Specifically, FMT from a subgroup of patients with MDD to microbiota-depleted rats induced a depression-like phenotype, including anhedonia and anxiety-like behaviors in the recipient animals, not observed in recipients of FMT from healthy control individuals. In addition, the results showed significant differences in the relative abundance of Firmicutes, Actinobacteria, and Bacteroidetes in gut microbiota compositions between depressed patients and healthy controls [25] [26].

Preclinical and clinical findings suggest an increasing trend of FMT in the management of cancer patients, and its use in oncology is encouraging. Data from colorectal cancer-bearing mice showed that FMT safely alleviated FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin)-induced intestinal mucositis [27]. Importantly, the functional impact of microbiota on cancer treatment efficacy has been documented, showing improved response to anti-PDL-1 immunotherapy in antibiotic-treated or GF mice bearing tumors after FMT from patients responding to cancer treatment compared to FMT from non-responders [28] [29]. Metagenomic analysis of fecal samples collected from mice treated with FMT from responding patients showed high diversity and abundance of *Ruminococcaceae/Faecalibacterium* [28]. Accordingly, Matson et al. suggested that the gut microbiome might have a mechanistic impact on antitumor immunity as “reconstitution of germ-free mice with fecal material from responding patients led to improved tumor control, augmented T cell responses, and greater efficacy of anti-PD-L1 therapy” [30].

Clinical studies concerning the use of FMT in cancer patients receiving high dose chemotherapy regimens prior to hematopoietic stem cell transplantation showed improved patients´ outcomes regarding the decrease of infectious complications, and graft-versus-host-disease, as recently reviewed [31]. However, no correlations towards cognitive, or cardiovascular functioning have been monitored. Currently, several clinical trials concerning the impact of FMT on the increasing cancer treatment efficacy are ongoing. According to the ClinicalTrials.gov database, the clinical trials NCT03341143 and NCT03353402 are assessing the effect of a fecal microbiota transplant from patients who responded to immunotherapy by PD-1 blockade to non-responding metastatic melanoma patients who failed immunotherapy. Furthermore, a clinical trial NCT04116775 addresses the anticancer effect of FMT from responders to pembrolizumab into non-responders in a cohort of patients with metastatic castration-resistant prostate cancer (http://clinicaltrials.gov/).

FMT might become a potential novel approach in the treatment of chemotherapy-related side effects on brain functions associated with intestinal microbiota disruption. However, further preclinical research focusing on the safety and efficacy of FMT is needed to increase the potential of application in the cancer population. Moreover, a documented case of FMT-related death in a cancer patient reinforces the need for more detailed and precise screening of donors for the presence of multi-resistant bacterial pathogens [32].

3. The Possible Impact of Diet and Physical Activity on the Gut Microbiome in Cancer Survivors

Diet represents an important factor influencing intestinal microbiota homeostasis. Malnutrition and changes in diet composition have been reported in cancer patients [33], and the potential link between the gut microbiome and

psychoneurological symptoms via microbiota-gut-brain communication has been proposed. Although the studies of diet–microbiota–cancer interactions are still very scarce, the impact of high-quality diet on PNS cluster and quality of life in breast cancer survivors have been intensively studied and widely reviewed [34]. A large cross-sectional study on breast cancer survivors (n=746) revealed that patients with a high-quality diet, defined as diets rich in fruits, vegetables, whole grains, and polyunsaturated fatty acids and low in added sugar, had lower levels of chronic inflammation compared to the survivors with the poorest diet quality [35]. A direct association of diet quality with subsequent mental and physical functioning was found in breast cancer survivors (n=714) who participated in the Health, Eating, Activity, and Lifestyle (HEAL) study [36]. Recently, Huang et al. demonstrated higher post-therapy cognitive scores regarding verbal fluency and improvements in delayed memory in breast cancer survivors with higher vegetable intake, tea-drinking, and fish oil supplementation [37].

Animal models, as well as clinical studies on elite athletes and healthy subjects, indicate the positive effect of physical activity on gut microbiota diversity and the production of beneficial metabolites [38]. Importantly, several clinical trials concerning cancer survivors reported the association between exercise and clinically meaningful improvements in quality of life [39] and mortality [40]. However, the relationship between exercise and gut microbiota in cancer survivors requires further investigation. Currently, a single-blinded, two-armed, randomized controlled trial aims to examine whether exercise favorably alters gut microbiota in the patients receiving androgen deprivation therapy for prostate cancer [41]. The results of ongoing clinical trials concerning the link between diet, physical activity, and microbiome alterations in cancer survivors (**Table 1**) may bring some interesting contributions to this field.

Table 1. Cancer survivorship and the microbiome. The table summarizes the list of ongoing and completed clinical trials dealing with the impact of the microbiome on cancer survivorship (according to **http://clinicaltrials.gov/**, accessed on 13 December 2020).

Study	Study Design	Disease	Purpose	Patients (*n*)	Intervention	Study Status
NCT03760653	A prospective, randomized double-blind study	Breast cancer survivors	To determine the effects of physical exercise together with the supplementation of a probiotic on the gut microbiota balance, the gut immune system, and quality of life (intended as functional and muscular capacity, physical qualities, and emotional state) in breast cancer survivors.	30	Physical exercise and probiotic group vs. probiotic group vs. placebo	Suspended (the project abandonment by the research who recruited the patients)

Study	Study Design	Disease	Purpose	Patients (*n*)	Intervention	Study Status
NCT04088708	A prospective, randomized, single-blind study	Breast cancer survivors	To determine exercise effects on the number, distribution, and types of bacteria in the gut of breast cancer survivors.	126	Aerobic exercise training vs. attention control	Ongoing
NCT02843425	A prospective, randomized, open-label, cross-over study	Colorectal cancer survivors	To determine the effect of pre-cooked beans on the levels of healthy bacteria in the digestive system and reduction in obesity effect on cancer risk.	80	Regular diet + beans, then regular diet—beans vs. regular diet—beans, then regular diet + beans	Active, not recruiting
NCT04097353	A prospective, randomized, open-label study	Pediatric cancer survivors	To examine the efficacy of Harvesting Hope for Kids (HH4K), a biobehavioral intervention delivered in the context of a university-based, cancer survivor garden to increase produce intake and physical activity in survivors and caregivers including changes in microbiome composition.	75	Harvesting Hope for Kids (HH4K) vs. Surviving Strong for Kids (SS4K)	Enrolling by invitation
NCT03781778	A prospective, randomized, double-blind study	Stage I-III colorectal cancer survivors	To test the effect of the consumption of foods made with resistant starch compared to foods made with corn starch on biomarkers that may be related to colorectal cancer progression in	NA	Resistant starch foods vs. foods with regular corn starch	Terminated (funding expiration)

Study	Study Design	Disease	Purpose	Patients (*n*)	Intervention	Study Status
			stage I-III colorectal cancer survivors.			
NCT04499950	A non-randomized, single-arm, phase II study	Breast cancer survivors	To determine the effects of pharmacotherapy and a remote behavioral weight loss intervention on weight loss in breast cancer survivors who are overweight or obese and the impact of successful weight loss on serum biomarkers and the gut microbiome.	55	POWER-remote behavioral weight loss intervention	Not yet recruiting
NCT01929122	A prospective, randomized, single-blind study	Colorectal cancer survivors	To explore the effects of cooked navy bean powder or rice bran consumption on the stool microbiome and metabolome of colorectal cancer survivors and healthy adults.	29	Cooked navy bean powder vs. rice bran vs. placebo	Completed

In conclusion, several clinical studies concerning the microbiota modulation in chemotherapy-treated survivors, as well as mounting research on mouse models and patients with neurological disorders and cardiovascular diseases outside the cancer field, suggest that targeting the gut microbiome might represent a perspective trend for improving the quality of life in cancer survivors. However, current clinical trials concerning the neuro- and cardioprotective effects of probiotics, or FMT are still rare, comprising mainly non-oncologic patients. Moreover, limitations in sample size, discrepancies in combinations of probiotic strains, and the length of treatment should be taken into account when considering the efficacy and safety of probiotic use. In the future, randomized controlled clinical trials on a large cohort of cancer survivors are highly warranted and could bring new perspectives for microbiota-mediated interventions to prevent or mitigate the chemotherapy-induced long-term effects.

Acknowledgment: The research was funded by the Slovak Research and Development Agency (APVV), grant number APVV-19-0411 and APVV-15-0086, and by the Scientific Grant Agency of the Ministry of Education,

Science, Research and Sport of the Slovak Republic and Slovak Academy of Sciences (VEGA), contract No. 2/0052/18 and 1/0327/19.

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