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REVERSAL OF INTESTINAL DYSBIOSIS MAY IMPROVE THE EFFECTIVENESS OF CHEMOTHERAPY AND RADIATION THERAPY IN CANCER TREATMENT

Kedar N. Prasad*

Engage Global Inc, 245 El Faisan Dr. San Rafael, CA 94903.

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***Corresponding Author: Dr. Kedar N. Prasad**
Engage Global Inc, 245 El Faisan Dr. San Rafael, CA 94903.

ABSTRACT
Chemotherapy and radiation therapy have produced increased 5-year survival rate in majority of cancers. However, acute toxicity during treatment remains a major problem. Therefore, new biological non-toxic strategy that can reduce acute side-effects of these therapies is needed. Intestinal dysbiosis (changes in the composition of bacterial population in favor of toxic bacteria) participates in the initiation and progression of cancer. It also increases the acute adverse effects of chemotherapy and radiation therapy and interfere with the effectiveness of these therapies. Therefore, reversing the intestinal dysbiosis by probiotics with prebiotics may decrease acute adverse effects during treatment and improve the effectiveness of these therapies.

KEYWORDS: Intestinal dysbiosis; Immune dysfunction; Side- effects; Probiotics; Cancer treatment.

1. INTRODUCTION

Chemotherapy and radiation therapy have produced increased 5-year survival rate in majority of cancers. However, acute toxicity during treatment remains a major concern of oncologists. Therefore, a novel non-toxic biological approach that can enhance the effectiveness of cancer therapies and reduce their acute adverse effects is needed.

Recent studies suggest that intestinal dysbiosis in which the composition of bacterial population changes in favor of toxic bacteria plays an important role in the initiation and progression of cancer, and the effectiveness chemotherapy and radiation therapy. In addition, it enhances chemotherapy and radiation therapy-induced acute adverse effects during treatment and reduces effectiveness of these therapies. The role of intestinal dysbiosis in affecting late adverse effects of therapies has not been evaluated. Intestinal dysbiosis is closely associated with the increased incidence of several types of cancer including, colorectal cancer, lung cancer, esophageal cancer, gastric cancer, hepatobiliary cancer, and pancreatic cancer.[1] The growth of harmful bacteria generates several harmful chemicals including proinflammatory cytokines which are toxic to the cells. The intestinal dysbiosis decreases the production of short-chain fatty acids such as butyric acid, propionic acid, and acetic acid butyric acid has diverse biological functions which include improving intestinal barrier integrity.[2] acting as an anti-cancer agent.[3] Intestinal dysbiosis also causes inflammation and enhances intestinal permeability. Therefore, reversing the intestinal dysbiosis by supplementation with probiotics with prebiotics would decrease the risk of development and rate of progression of cancer, and improve the effectiveness of therapeutic agents, and reduce their acute adverse effects during treatment. The presence of beneficial bacteria such as strains of *Lactobacillus* and *Bifedo* play an important role in maintaining healthy gut by producing certain B-vitamins, vitamin K1, short-chain fatty acids such as butyric acid, certain essential amino acids, neurotransmitters, and improving immune response and emotional and cognitive functions.[4]

This review briefly describes role of intestinal dysbiosis in in the development, progression, and treatment of several types of cancer. Therefore, we propose that reversal of intestinal dysbiosis by probiotics with prebiotic may reduce acute adverse effects of chemotherapy and radiation therapy and improve their effectiveness.

2. Role of Intestinal Dysbiosis in Colorectal Cancer (CRC)

Colorectal cancer (CRC) is the second most common cause of cancer death. In 2023, approximately, 153, 020 cases of this form of cancer would be diagnosed, and 52,500 of them will die of this disease.[5] Current

treatments involve surgery for resectable CRC, and chemotherapy, radiation therapy, immunotherapy, and their combination for non-resectable tumor. Despite these valuable treatments, approximately 50% of the patients develop incurable recurring CRC.[6] The exact reasons are not known; however, growing evidence suggest that cancer treatment agents can enhance the levels of already existing intestinal dysbiosis that can interfere with the effectiveness of treatment and eventually making cancer resistant to therapy. Some studies are presented here.

Intestinal dysbiosis occurs in patients with CRC which is evidenced by the observation in which *Fusobacterium nucleatum* is a gram-negative spore-free anaerobic bacteria present in abundance in the tissue and stool samples of patients with CRC.[7] The levels of these bacteria were higher in CRC carcinoma than in normal colon tissue, and they were very enriched in adenomas.[8] These pathogenic bacteria promote progress of CRC and is associated with poor prognosis and drug resistance.[9] Toxic form of *Bacteroides fragilis* are another anaerobic gram-negative bacterium in the gut which secretes toxins that can destroy epithelial barrier in the gut, induce inflammation and precancerous lesions, and promote initiation and progression of CRC.[10]

3. Role of intestinal dysbiosis in lung cancer

Lung cancer is one of the most serious malignancies which is increasing world-wide. The levels of beneficial bacteria *Actinobacteria species and Bifidobacterium species* were lowered, while the level of harmful bacteria *Enterococcus species* was enhanced in patients with lung cancer.[11] Intestinal dysbiosis is associated with the progression of lung cancer.[12]

4. Role of intestinal dysbiosis in breast cancer

Female breast cancer is most common worldwide (The 2020 Global Cancer Statistics Report). There are different subtypes of breast cancer which include ER (estrogen receptor) positive, progesterone receptor (PR) positive, and HER2 (human epidermal growth factor receptor2) negative. These types of breast cancer are characterized by low invasiveness, a low recurrence rate, a high survival rate, and the best response to hormone therapy.[13,14] Another subtype of breast cancer is ER and PR positive, HER2 negative. This type of breast cancer has a highest relapse rate and lower survival.[15] HER2 positive breast cancer showed increased survival rate with target therapy.[16] The triple negative breast cancer (ER, PR, and HER2 negative) has a high risk of relapse.[17]

It has been reported that a distinct microbial pattern was associated with each subtype of breast cancer. For example, the invasive ductal carcinoma had abundance of harmful bacteria such as *Tepidiphilus, Alkanindiges, Stenotrophomonas*, while invasive lobular carcinoma had abundance of *peptostreptococcus, Micromonospora, Faecalibacterium, and Stenotrophomonas*. However, their bioinformatic analysis revealed that *Porphyromonas, Lacibacter, Ezakiella, and Fusobacterium* were abundant at more advanced stage of the disease compared to lower stage.[18] suggesting the role of intestinal dysbiosis in the progression of breast cancer. An oral pathogen *Fusobacterium nucleatum* could migrate via the blood stream and accumulate in breast cancer causing increased progression of the disease.[19] This observation suggests that suppression of *F. nucleatum* may enhance the treatment of breast cancer.[20] Another study reported that the presence of toxic *Bacteroides fragilis* in the gut or breast tissue may increase the aggressiveness of breast tumor leading to metastasis to distant organ.[21]

5. Role of intestinal dysbiosis in leukemia

Acute leukemia is a common hematological malignancy. The composition of gut microbiota influences initiation and progression of acute leukemia, as well as treatment outcome, side effects, and prognosis of the disease.[22] Intestinal dysbiosis, which occurs in leukemia, causes damage to the intestinal epithelial barrier which allows migration of harmful bacteria to the blood stream or lymph node that leads to inflammatory immune response which may contribute to the development of cancer.[23,24] Intestinal dysbiosis is also associated with the development acute lymphocytic leukemia [25] Several studies have suggested that intestinal dysbiosis occurs during the onset and treatment of leukemia, and this may reduce the effectiveness of treatment and may predict poor prognosis.[22]

6. Role of intestinal dysbiosis in prostate cancer

Diet, drugs, disease, genetics, and antibiotic can induce intestinal dysbiosis. It has been suggested that antibiotic treatment activates the inflammatory signaling pathway which contributes to progression of prostate cancer. This was confirmed by experiments which showed that antibiotic-induced intestinal dysbiosis promoted the growth of prostate cancer in a murine model by activating NF-kB-STAT3-IL-6 pathway. In addition, antibiotic treatment markedly increased the number of *Proteobacteria* which is a marker of intestinal dysbiosis.[26] Both NF-kB and STAT3 (signal transducer and activator of transcription 3) are transcriptional factors which increase the expression of pro-inflammatory cytokine IL-6.

Analysis of feces from patients with prostate cancer showed the presence of intestinal dysbiosis as evidenced by increase in the number of *Bacteriodes, Streptococcus, Rikenellaceae, Alistepes, and Lachomospira* which increase the production of lipopolysaccharide which causes growth of prostate cancer cells, and play a role in the development of castration-resistance prostate cancer.[27,29]

7. Role of intestinal dysbiosis in brain cancer

The nuclear factor kappa-B (NF-kB) enhances production of inflammatory cytokine IL-6 and IL-8 which activates survival genes in glioblastoma. High

expression of NF-kB is associated with poor survival of patients with mesenchymal glioblastoma.[30,31] Intestinal dysbiosis inhibits the brain immune function which can affect all stages of brain cancer development and helps tumor cells to evade immune surveillance.[32] Oral dysbiosis is associated with the malignant brain tumor.[33] Oral dysbiosis can influence the activity of intestinal dysbiosis,[34] and together they can further help in the development and progression of brain tumor. The intestinal dysbiosis contains abundance of *Enterobacteria ceae* in meningioma which suppresses short-chain fatty acid (SCFA) producing bacteria and causes immune dysfunction and unhealthy intestinal environment.[35] The genus *Escherichia/Shigella* were present in large amounts in the brain tumor that can promote chronic inflammation in the brain. The genus *Fusobacterium* and *Akkermansia* are present in in the intestinal dysbiosis that participates in the development and progression of glioma.[7,32]

8. Role of intestinal dysbiosis in melanoma

Skin microbiome with abundance of beneficial bacteria may increase the immunity of the skin and protect the host against onset of skin inflammatory disorders, infections, and wounds.[36,38] On the other hand, skin dysbiosis and intestinal dysbiosis may play a role in the development and progression of skin melanoma in animal model.[39]

9. Radiation therapy enhances the levels of existing intestinal dysbiosis

It has been reported that radiation therapy enhances the levels of existing intestinal dysbiosis as evidenced by increased number of harmful bacteria such as *proteobacteria and Fusobacteria* and decreased number of beneficial bacteria such as *Biofedobacterium and Faecalibacterium*.[40,41] In addition, chemotherapy and radiation therapy also enhance the levels of intestinal dysbiosis in cancer patients.[42,43]

10. Chemotherapy enhances the levels of existing intestinal dysbiosis.

Chemotherapeutic drugs can directly increase the levels of existing intestinal dysbiosis which damages intestinal epithelial cells, reduce absorption and metabolism of drugs, increase the toxicity of drugs, and reduce their efficacy.[22] Methotrexate (MTX) is widely used in the treatment of leukemia. MTX treatment decreases the population of *Bacteroides fragilis*.[44] After chemotherapy the composition of bacterial population is altered such as the number of *Bacteroides fragilis* decreased, whereas other bacteria such as *clostridiaceae and Streptococcaceae* increased in children with acute lymphoblastic leukemia.[45] Reversal of dysbiosis may improve prognosis of the disease. A randomized controlled trial involving 60 children with acute leukemia revealed that patients who took prebiotics during chemotherapy had significant reduction in most gastrointestinal side-effects including vomiting, nausea, abdominal distension, constipation, and abdominal pain.[46]

11. Impact of Intestinal dysbiosis During and After Chemotherapy and Radiation therapy

As mentioned in the above two paragraphs, radiation therapy and chemotherapy induce intestinal dysbiosis. Since intestinal dysbiosis is already present in patients with cancer these therapeutic agents further aggravate the levels intestinal dysbiosis which is associated with acute gastrointestinal discomforts that include diarrhea, mucositis, and late adverse effects such as psychoneurological changes, cancer cachexia, and fatigue[47] Intestinal dysbiosis may enhance development and progression of acute and late adverse effects which impact quality of life during and after treatment as well as survival of patients.[48-51]

12. Supplementation with Probiotics/Prebiotics Reverses Intestinal Dysbiosis That Reduces Acute Side-Effects during Treatment

The main function of probiotics is to restore the balance of bacterial population in favor of beneficial bacteria in the intestine. Prebiotics are soluble and insoluble fibers which provide substrate for fermentation by the beneficial bacteria to produce short-chain fatty acids such as butyric acid which exhibits diverse biological function including anti-cancer.[3,52]

Supplementation with probiotics with prebiotics may be useful in reducing the side effects of chemotherapy and radiation therapy which include decreased risk of infections and improved in recovery of gut damage induced by drugs and its proper function[53] In addition, probiotics can bind with mutagens and degrades them, lowers intestinal pH, and secrets anti-inflammatory molecules.[24] In a clinical study, supplementation with probiotics containing strains of *lactobacillus* and *Bifedobacterium* alone before chemotherapy and radiation therapy prevented gastrointestinal mucositis. Administration of prebiotics alone before radiation therapy had no impact on the diarrhea in patients with pelvic cancer.[54]

Therefore, it is essential that probiotics with prebiotics should be utilized for reducing acute adverse side-effects of cancer treatment. In addition, 60-70% of certain beneficial bacteria such as strains of *Lactobacillus* and *Bifedo* when administered orally is destroyed in the acid pH of the stomach, and more are inactivated in the bile acid of the intestine. This necessitates to add acid resistance probiotics such as *Bacillus coagulans*. The use of such probiotics with prebiotics may reverse intestinal dysbiosis, and thereby, reduce some of the acute adverse effects of chemotherapy and radiation therapy.

13. CONCLUSIONS

Chemotherapy and radiation therapy have produced increased 5-year survival rate in majority of cancers, but they caused acute toxicity during treatment. Intestinal

dysbiosis play an important role in initiation and progression of cancer. In addition, it interferes with the effectiveness of these therapies and enhances acute adverse side-effects during treatment. We propose that oral supplementation with probiotics with prebiotics would reverse intestinal dysbiosis and improve the effectiveness of chemotherapy and radiation therapy by reducing their acute toxicity during treatment. Clinical studies should be performed to test this hypothesis.

Declaration

Conflict: Kedar N Prasad is a retired Professor from the University of Colorado School of Medicine, and currently is a Chief Scientific Officer of the Engage Global, Inc, Provo, Utah. This company sells nutritional products to consumers.

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