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CANCER THERAPIES AND THEIR IMPACT ON THE GUT MICROBIOTA

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Abstract: This article is a review of the relevant literature published between April 2019 and March 2020 on the impact of cancer therapy on the gut microbiota and the effects of microbiota modulation on the outcome of cancer treatment. The decrease in richness and diversity of the gut microbiota is associated with a higher rate and degree of side effects in patients undergoing classic systemic chemotherapy. In patients receiving immuno-therapy, higher diversity of the gut microbiota is associated with treatment response, often then resulting in prolonged survival. Studies confirmed a negative impact of antibiotic treatment on the response to immuno-therapy and respective patient outcomes. Part of these effects seem to be mediated by a direct interaction between the gut microbiota and local immune cell populations in the intestinal mucosa, in particular T-cell and macrophage populations. A less diverse gut microbiota was also associated with a higher prevalence of side effects of radio-therapy treatment. Data from animal experiments indicate beneficial effects of antibiotic treatment prior to radiotherapy, which is in contrast to the data from patients receiving immuno-therapy. Studies published within the timeframe addressed in this review suggest that faecal microbiota transplantation can improve treatment-induced diarrhoea. In haematological malignancies, chemotherapy and allogeneic hematopoietic cell transplantation lead to decreased richness and loss of diversity of the gut microbiota. As expected, the lowest microbiota diversity was seen in patients receiving antibiotics. A lower diversity before and after cancer treatment was associated with poor survival. The gut microbiota may serve as a target for manipulating the immune outcome response to different cancer treatment modalities with the aim to improve the efficacy of oncological therapy.

Keywords: Gut microbiota, Cancer, Chemotherapy, Immuno-therapy, Radiotherapy, Allogeneic hematopoietic cell transplantation.

INTRODUCTION

The overall survival of cancer patients has improved during the last two decades due to progress regarding modern oncological therapy. However, side effects of cancer treatment are very common including loss of appetite, fatigue, and diarrhoea, which can lead to a reduced quality of life and even death[1]. Side effects often lead to an increase in hospitalization rates and time spent as an inpatient, an increase in related costs, a decrease in the patient's compliance with treatment, and as a consequence alteration of the treatment plan[2].

Evidence suggests that chemotherapy and radiation treatment induce changes in the composition of the gut microbiota that are closely related to intestinal inflammation[3,4]. The gut microbiota plays an important role in the maintenance and modification of the intestinal barrier function, the mucosal immune response and local repair mechanisms[5,6]. A better understanding of the mechanisms involved in the modulation of the gut microbiota induced by different treatment modalities will help finding new therapeutic solutions and identify predictive markers for relevant side effects and for prognosis of cancer therapy. The current article is a review of the literature published between April 2019 and March 2020 on the impact of cancer therapy on the gut microbiota and the effects of the disruption in the gut microbiota on the outcome of the respective patients.

ROLE OF THE MICROBIOTA IN THE THERAPY OF SOLID CANCERS

Impact on Chemotherapy

5-Fluorouracil (5FU)-based chemotherapy is widely used in the treatment of colorectal cancer (CRC). The drug and its derivatives improve the overall survival of patients; however, it induces intestinal mucositis in about 50-80% of patients[7]. A study[8] was carried out in mice using the azoxymethane/dextran sodium sulphate (AOM/DSS) model of CRC to characterize the effects of 5FU on colon inflammation and to determine whether the gut microbiota can influence this response. Chemotherapy decreased the richness and evenness of the gut microbiota in this model. The relative abundance at the operational taxonomic unit level was decreased in the classes *Coriobacteria* and *Deltaproteobacteria* and increased in *Actinobacteria, Bacilli, Betaproteobacteria,* and *Verrucomicrobia*. A decrease in abundance of the phylum *Firmicutes* was found in AOM/DSS mice treated with 5FU but not in those with AOM/DSS alone. The expression of a selected panel of inflammation related genes was significantly elevated in 5FU treated mice. A decrease in circulating immune cells including neutrophils and monocytes was observed with 5FU treatment. Faecal microbiota transplantation (FMT) from 5FU treated mice to control mice demonstrated that 5FU induced changes in the microbiota can alter colon inflammatory markers[8].

Another study[9] examined the association between the gut microbiota and diarrhoea in CRC patients receiving the CapeOX regimen. Richness and diversity of the gut microbial community were lower in patients with diarrhoea than those without diarrhoea. *Klebsiella pneumoniae* was most prevalent in the chemotherapy induced diarrhoea group (35% compared to only 3% in the group without diarrhoea). The authors also identified 23 pathways associated with microbial metabolites, cell proliferation and death, immune system, and other aspects that might be involved in the pathogenesis of diarrhoea[9].

There is still a lack of drugs that can be used for treatment of intestinal mucositis caused by 5FU. A study using a rat model investigated the effect of berberine (BBR), an isoquinoline alkaloid, in this setting[10]. Inflammatory cytokines, faecal metabolites and the gut microbiota were significantly altered after BBR administration. BBR reversed the changes in the gut microbiota induced by 5FU. The drug increased the relative abundance of *Firmicutes* and decreased *Proteobacteria.* Beneficial bacteria were markedly enriched after BBR treatment, including *Lactobacillus*, *Clostridium* and *Ruminococcus*. Meanwhile, the level of pathogenic bacteria such as *Escherichia* and *Shigella* was reduced. FMT from BBR treated rats reversed diarrhoea, reduced the inflammatory response in the ileum, and improved the intestinal mucosal barrier function in rats with 5FU induced colitis.

Sorafenib is a tyrosine kinase inhibitor used as standard treatment to improve the prognosis of patients with advanced hepatocellular carcinoma (HCC). The association of adverse effects of sorafenib treatment [hand-foot syndrome (HFS) or diarrhoea] with the gut microbiota was evaluated in a study carried out in Japan[11]. Before treatment, faecal samples from patients with HCC were analysed. Patients without HFS had a higher relative abundance of oral origin bacteria such as *Veillonella*, *Bacillus*, and *Enterobacter* than those patients with Sorafenib-induced HFS. This might furthermore affect the enterohepatic recycling of sorafenib and reduce the serum drug levels. Compared to patients with diarrhoea, the non-diarrhoea group had a higher relative abundance of *Butyricimonas*, which is a butyric acid-producing bacterium that can protect against mucosal inflammation. There was also a lower abundance of *Citrobacter*, *Peptostreptococcus*, and *Staphylococcaceae* in the non-diarrhoea group. These data indicate that patients with a favourable gut microbiota are less likely to develop Sorafenib-induced diarrhoea in the course of treatment.

Impact on Immuno-Therapy

Several studies have established a link between the outcome of patients on immuno-therapy, mainly immune checkpoint inhibitors (ICI), and treatment response. This has mainly been studied in non-small cell lung cancer (NSCLC). Stool samples had been collected from NSCLC patient participating in the CheckMate078 and CheckMate870 trials investigating the effect of the anti-PD-1 blocker nivolumab. Faeces was collected prior to treatment initiation, at treatment initiation, at clinical follow-up visits and at the time of disease progression. The ma-

terial of 37 patients was further analysed and there was a higher microbial diversity in stool samples of responders when compared with non-responders defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[12]. There was also prolonged progression-free survival (PFS). Responders showed intestinal enrichment of *Alistipes putredinis*, *Bifidobacterium longum*, and *Prevotella copri*, whereas *Ruminococci* were more abundant in non-responders[12]. Similar results were demonstrated in melanoma patients[13]. Longer PFS was associated with *Faecalibacterium prausnitzii*, *Coprococcus eucactus*, *Prevotella stercorea*, *Streptococcus sanguis*, *Streptococcus anginosus*, and *Lachnospiraceae* bacterium 3 1 46FAA, and the worse outcome was associated with the abundance of *Bacteroides ovatus*, *Bacteroides dorei*, *Bacteroides massiliensis*, *Ruminococcus gnavus*, *Blautia producta*. In addition to 16S RNA gene sequencing, the authors used shotgun metagenome sequencing to identify clusters defining three groups associated with different prognosis and risk of progression as well as distinct relevant metabolic pathways being active in these groups[13]. A further study[14] recommended the analysis of the patients' bowel habits as an indicator of their gut microbiota and associated treatment outcome.

In line with these findings, numerous studies have confirmed a negative impact of antibiotic treatment on the response to ICI. Retrospective assessment of 234 Korean patients who received immuno-therapy for a variety of solid tumours showed a decrease in the objective response rate in patients who received antibiotics prior to their tumour-directed treatment (OR 0.47; 95% CI: 0.225-0.968)[15]. Both PFS and overall survival (OS) were significantly shorter in these patients, with this effect being confirmed in multivariate analysis. Antibiotic treatment was an independent prognostic predictor (PFS: HR 1.72, 95% CI: 1.264-2.326; OS: HR 1.785, 95% CI: 1.265-2.519)[15]. A further retrospective study on 102 patients with solid tumours looked at the pattern of antibiotics intake in relation to the outcome under ICI treatment[16]. There was no overall difference detected between patients who had antibiotics four weeks prior to or after treatment initiation, and the general effect of antibiotics was not significant in this study. However, patients with higher antibiotics exposure again showed significantly lower PFS and OS. This impact of antibiotic treatment on lowered response rates resulting in shorter PFS and OS has been investigated primarily in NSCLC[17,18], but also in renal cell cancer (RCC)[19], and melanoma[20]. Use of antibiotics up to 30 days prior to treatment with both anti-PD1 and anti-CTLA4 blockers caused primary resistance against the tumour treatment and significantly worse outcome (PFS: HR 0.32, 95% CI: 0.13-0.83; OS: HR 0.52, 95% CI 0.21-1.32). There are attempts to identify the "vulnerable" phase during which antibiotics have this deleterious effect, but this has not yet been clearly defined[21]. A prospective multicentre cohort study on 196 patients with NSCLC, melanoma and other solid tumours looked at the difference between patients receiving antibiotics prior to ICI application *vs.* those receiving antibiotic drugs concomitant with their immuno-therapy-[22]Setting, and Participants: This prospective, multicenter, cohort study conducted at 2 tertiary academic referral centers recruited 196 patients with cancer who received ICI therapy between January 1, 2015, and April 1, 2018, in routine clinical practice rather than clinical trials. Main Outcomes and Measures: Overall survival calculated from the time of ICI therapy commencement and radiologic response to ICI treatment defined using the Response Evaluation Criteria in Solid Tumors (version 1.1. While there was no significant impact by concomitant antibiotic treatment, patients with prior exposure were more likely to be refractory to immuno-treatment (81% *vs.* 44%, $p<0.001$), resulting in significantly worse OS with similar effects across tumour entities. The use of antibiotics prior to ICI treatment was an independent predictor of worse tumour response in multivariate analysis (HR 8.2, 95% CI: 4.0-16.9)[22]. By contrast, a recent meta-analysis[23] reported no relevant difference in the effect of different antibiotic exposure pattern in relation to immuno-therapy administration in NSCLC and RCC patients. The effect of antibiotics has also been assessed by blood-based analysis of the microbiota, utilizing serum citrulline as a surrogate marker[24]. Use of antibiotics was associated with lower citrulline levels, and presence of *Peptostreptococcae*, *Paludibaculum*, *Lewinella* with the response to treatment. Detection of *Gemmatimonadaceae* was associated with progression. Antibiotics do not only affect tumour response to ICI but have also an impact on adverse drug effects. A retrospective analysis[25] of 826 patients revealed a higher incidence of ICI mediated diarrhoea and colitis in patients who had received antibiotics.

Significant effort has been made to understand the pathophysiological link between the gut microbiota and the response to immuno-therapy (to ICIs in particular). Studies[26] of patients with colorectal cancer demonstrated a direct interaction between the local immune cell populations and the composition of the gut microbiota. *Bacteroides* and *Faecalibacterium* were increased in patients with high numbers of specific regulatory T cells (Tregs), and *Faecalibacterium*, *Ruminococcaceae*, *Eubacterium* and *Bacteroides* were associated with a high distribution of certain tumour-associated macrophages[26]. This indicates the role of the local microbiota as immune-modulators, most likely immune-suppressors. Bachem et al demonstrated the impact of microbiota on the memory function of CD8+ T cells[27]. This was mediated by short-chain fatty acids (SCFA), mainly butyrate, which are required for an optimal T cell response. Among other factors, a change in SCFA metabolites has been identified in analyses of the gut metabolome of NSCLC patients under anti-PD1 treatment with nivolumab[28]. Similarly, NSCLC patients on nivolumab showed a higher frequency of unique memory CD8+ T cells as well as natural killer (NK) cells in the periphery as a response to anti-PD1 treatment[12]. Since the gut microbiota has an influence on these mechanisms, data from mice show that treatment with probiotics (*Lactobacillus reuteri*) can reduce adverse effects (e.g., colitis) of ICI treatment[29].

Impact on Radiotherapy

There is no doubt that the intestinal microbiota influences the effects of radiotherapy, but the precise interplay of the factors involved requires further elucidation. The prospective MARS study analysed the influence of the gut microbiota on radiotherapy induced gastrointestinal side-effects in three different cohorts[30]. Patients without post-radiation gastrointestinal symptoms had a higher pre-treatment microbial diversity. Low diversity was also linked to late onset radio-enteropathy. Enteropathy in these patients was defined as both patient-related outcome (based on reported symptoms) and clinician-reported outcome (based on clinical findings) and was associated with a change of the interleukin pattern and higher counts of *Clostridium* IV, *Roseburia* and *Phascolarctobacterium*[30]. The abundance of *Roseburia* and *Propionibacterium* inversely correlated with IL15 levels. A significantly reduced α-diversity alongside increased β-diversity was also reported by Wang et al[31] analysing faecal samples of patients undergoing pelvic radiotherapy for cervix cancer. The high abundance of *Proteobacteria* and *Gammaproteobacteria* and low abundance of *Bacteroides* were seen in patients with radiation enteritis, whereas *Coprococcus* was high at baseline in patients who subsequently developed enteritis. A co-culture model showed epithelial inflammation and epithelial barrier dysfunction with enhanced TNFα and IL1β expression when cells were exposed to microbiota derived from patients with radiation enteritis[31]. Notably, patients of differing ethnic backgrounds showed different microbiota profiles even in the case of a similar baseline α-diversity before radiotherapy[32]. These changes also resulted in shifts in the metabolomic analyses of the same cohorts. It is likely that this affected not only local side effects such as enteritis but also systemic effects such as fatigue[33]. While there were no distinct effects prior to or after radiotherapy, α-diversity was significantly lower mid-cycle in patients with fatigue. *Proteobacteria*, *Firmicutes* and *Bacteroidetes* were dominant in patients with fatigue with *Escherichia*, *Bacteroides*, *Faecalibacterium* and *Oscillospira* genera being most abundant[33].

Efforts were also made to extract clinical use from this knowledge. A pilot study[34] on FMT in patients with chronic radiation enteritis showed reduced toxicity after 8 weeks and improvement of diarrhoea, rectal bleeding, pain and incontinence. In contrast to the data from immuno-therapy studies mentioned above, studies in mice undergoing radiation treatment showed better restitution of the mucosal integrity and survival when pre-treated with antibiotics[35]. Antibiotics reduced lipopolysaccharide exposure and hence the activation of the TLR4/MyD88/NFκB pathway-axis. In addition to this modulation of the local inflammatory processes, TGFβ dependant signalling was also reduced, leading to less fibrotic changes[35]. Similarly, vancomycin enhanced the radiotherapy-induced anti-tumour response in mice with the effect being dependant on tumour associated antigen cross presentation by dendritic cells (DCs) to cytolytic CD8+ T cells and presence of IFNγ[36]. In this setting, application of butyrate, usually produced by the vancomycin depleted microbiota, abrogated this effect. In contrast, admin-

istration of valeric acid resulted in a beneficial effect with better survival and improved intestinal epithelial integrity in mice[37].

In human patients undergoing multimodal treatment for cervical cancer, administration of amylase resistant starch (in the form of prebiotics) showed only a minor effect[38]. The frequency of clinical proctitis was similar between the treatment and placebo group, and there was only a minor improvement in the functional impact and related symptoms at 4 weeks after treatment completion. These differences were not present at 6 weeks post-treatment[38]. By contrast, administration of probiotics (in this study a combination of *Bifidobacterium longum*, *Lactobacillus lactis*, and *Enterococcus faecium*) seems to have a beneficial effect on oral mucositis after radiotherapy of head and neck cancer[39].

Role of the Microbiome in the Treatment of Haematological Malignancies

Intestinal mucositis is a common side effect of chemotherapy for haematological malignancies. A prospective study describing weekly changes in the intestinal microbiota during chemotherapy of childhood acute lymphoblastic leukaemia (ALL) found lower α-diversity of the gut microbiota in patients compared to siblings at baseline[40], with further decreases reported during the treatment period. Low α-diversity and high abundance of unclassified *Enterococcus spp.* were associated with low plasma citrulline and high plasma C-reactive protein (CRP) levels, while high abundance of unclassified *Lachnospiraceae spp.* was associated with high citrulline and low CRP levels suggesting a potential protective role of these bacteria against intestinal barrier injury and systemic inflammation. *Lachnospiraceae* species produce short-chain fatty acids including butyrate from dietary fibre, which improves epithelial barrier function and inhibits the production of pro-inflammatory cytokines.

A case-control study[41] of 32 patients with ALL and 25 healthy siblings showed that the microbiota diversity and richness was significantly lower in patients than in their siblings at diagnosis and during chemotherapy, with the lowest microbiota diversity documented in patients receiving antibiotics. The abundance of *Lachnospiraceae* increased consistently during chemotherapy. Also, an increase of the mucolytic, Gram-positive, anaerobic bacteria *Ruminococcus gnavus* and *Ruminococcus torques* was observed which was thought may contribute to the development of mucositis. A year after the start of chemotherapy, the gut microbiota remained altered[41].

Another study[42] analysed the predictive capacities of the gut microbiota as a biomarker for the risk of infection during induction chemotherapy in patients with acute myeloid leukaemia (AML). At the start of treatment, higher stool α-diversity (Shannon index) and higher relative abundance of *Porphyromonadaceae* were inversely associated with the cumulative incidence of infection during induction chemotherapy. Patients receiving carbapenems for more than 72 hrs prior to neutrophil recovery had significantly lower α-diversity at neutrophil recovery and were approximately 4 times more likely to have an infection in the 90 days following neutrophil recovery.

Allogeneic hematopoietic cell transplantation (allo-HCT) is often used for the treatment of haematological malignancies. A study compared the impact of intensive chemotherapy and allo-HCT on the microbiota[43]. Both patient groups had heavy but comparable antibiotic exposure and showed some similarities regarding dysbiosis. The microbial diversity declined in both groups markedly, but at a faster rate in the allo-HCT cohort, with *Enterococcus* dominating in low-diversity samples in both cohorts. Increased abundance of *Lactobacillus* was observed in low-diversity communities in the chemotherapy group but not in the allo-HCT cohort. Future research is needed to determine whether the domination of *Enterococcus* or *Lactobacillus* predicts different clinical outcome.

The associations between specific microbial taxa, host immune markers, immune cell reconstitution, and clinical outcome were studied in children undergoing allo-HCT[44]. High concentrations of the antimicrobial peptide human beta-defensin 2 were associated with the development of moderate or severe acute graft-versus-host disease and high mortality in patients with high abundances of *Lactobacillaceae*. Rapid reconstitution of NK and B cells together with high abundances of obligate anaerobes such as *Ruminococcaceae* prevented the development of acute graft-versus-host disease and death. A predominance of *Clostridiales*, represented by

Ruminococcaceae and *Lachnospiraceae*, did not persist after transplantation in patients who developed moderate or severe acute graft-versus-host disease or in those patients who died. More severe inflammation was associated with high abundances of facultative anaerobic bacteria such as *Enterobacteriaceae*. Antimicrobial treatment significantly affected the gut microbiota. Treatment with vancomycin and ciprofloxacin was associated with reduced *Clostridiale*s and increased abundances of facultative anaerobic *Enterobacteriaceae*[44].

The role of the microbiota in the prediction of death after allo-HCT was studied in a multicentre study[45] carried out in the USA, Germany, and Japan. Similar changes in the gut microbiota during allo-HCT, namely, loss of diversity and domination by single taxa, were observed across all centres. The lower-diversity compositions were characterized by an abundance of *Enterococcus*, *Klebsiella*, *Escherichia*, *Staphylococcus*, and *Streptococcus*. Higher diversity of the gut microbiota was associated with a lower risk of death (HR 0.71, 95% CI: 0.55-0.92). Not only diversity but also a signature of specific bacterial abundances predicted the risk of death after allo-HCT.

CONCLUSIONS

The studies reviewed confirm an important role of the gut microbiota in the pathogenesis of adverse effects of different modalities of cancer treatment. This includes an impact on intestinal and systematic inflammation, the local immune response, and affects the clinical outcome after chemotherapy, allo-HCT, immuno-therapy and radiotherapy. Higher microbial diversity is associated with prolonged progression-free and overall survival in most settings. Antimicrobial treatment before and during chemotherapy and immuno-therapy significantly affects the gut microbiota, resulting in an altered response to treatment and worse prognosis. Longitudinal profiling of the microbiome could help to identify patients at risk of adverse effects, including infections or other effects related to a poor immune response. Future research is needed to determine microbial taxa most related to side effects of cancer therapy and what interventions can be used to restore the respective microbiota.

Conflict of Interest

The authors declare no conflict of interest.

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