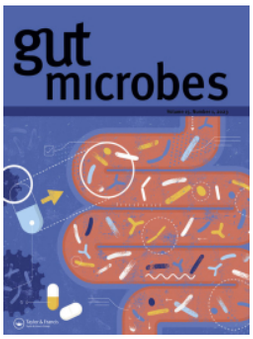

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REVIEW

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Pharmacomicrobiomics of cell-cycle specific anti-cancer drugs – is it a new perspective for personalized treatment of cancer patients?

Karolina Kaźmierczak-Siedlecka[a], Nikola Bulman[a], Paweł Ulasiński[b], Bartosz Kamil Sobocki[c], Karol Połom[d], Luigi Marano[d], Leszek Kalinowski[a,e], and Karolina Skonieczna-Żydecka[f]

[a]Department of Medical Laboratory Diagnostics – Fahrenheit Biobank BBMRI.pl, Medical University of Gdansk, Gdańsk, Poland; [b]Unit of Surgery with Unit of Oncological Surgery in Koscierzyna, Kościerzyna, Poland; [c]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdańsk, Poland; [d]Academy of Medical and Social Applied Sciences, Elbląg, Poland; [e]BioTechMed Centre/Department of Mechanics of Materials and Structures, Gdansk University of Technology, Gdansk, Poland; [f]Department of Biochemical Research, Pomeranian Medical University in Szczecin, Szczecin, Poland

ABSTRACT

Intestinal bacteria are equipped with an enzyme apparatus that is involved in the active biotransformation of xenobiotics, including drugs. Pharmacomicrobiomics, a new area of pharmacology, analyses interactions between bacteria and xenobiotics. However, there is another side to the coin. Pharmacotherapeutic agents can significantly modify the microbiota, which consequently affects their efficacy. In this review, we comprehensively gathered scientific evidence on the interplay between anticancer therapies and gut microbes. We also underlined how such interactions might impact the host response to a given therapy. We discuss the possibility of modulating the gut microbiota to increase the effectiveness/decrease the incidence of adverse events during tumor therapy. The anticipation of the future brings new evidence that gut microbiota is a target of interest to increase the efficacy of therapy.

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Introduction

The gut microbiome has been analyzed in multiple aspects, especially over the last several years. Recently, many communication mechanisms between microorganisms residing in particular parts of the human body and distal organs have been described. It is known as an "axis." For instance, the gut – brain axis, gut – liver axis, gut – muscle axis, gut – bone axis, and others.[1–4] Currently, some data indicate that there is also a bidirectional communication between drugs and the gut microbiome.[5] It means that gut microbes have an impact on individuals' response to drugs, whereas drugs affect the gut microbiome. Overall, these interactions are now collectively known as the term "pharmacomicrobiomics". Gut microbes are able to change the bioavailability, bioactivity, and toxicity of drugs.[5] The gut microbiota interacts with drugs with respect to their pharmacokinetics and pharmacodynamics.[6,7] Drug metabolism, which is a part of pharmacokinetics, may be mediated by gut microbes both directly (by converting drugs into active/inactive or toxic metabolites) and indirectly (via microbiota-derived metabolites).[6] Gut microbiome may also affect drug-drug interactions and even induce those interactions. Supplementation of probiotics (some of them are registered as drugs depending on country regulations) allows the analysis of gut microbes as drugs. For instance, yeast *Saccharomyces boulardii* CNCM I-745 is registered as a probiotic drug in Poland. The selected bacteria significantly altered the response to the treatment. *Akkermansia muciniphila* (next-generation probiotic, postbiotic) may affect the efficiency of anti-cancer treatment regarding immunotherapy through enhancement of CTLA-4 and PD-1/PD-L1 blockade.[8–10] Overall, the gut microbiome influences the functioning of immune system both systemically and locally, contributing to the maintenance of intestinal homeostasis.[11] Thus, microbial community may affect the response to the immunotherapy in different tumors regarding also breast cancer.[8,12,13] The influence of drugs on the gut microbiome is

CONTACT Leszek Kalinowski leszek.kalinowski@gumed.edu.pl Department of Medical Laboratory Diagnostics – Fahrenheit Biobank BBMRI, Medical University of Gdansk, 7 Dębinki street, Gdańsk 80-211, Poland

observed in alteration of gut microbiome composition (for instance, by proton pump inhibitors) and its function (by metformin).[14] Both the composition and production of microbiota-derived metabolites (for instance, SCFAs – short-chain fatty acids) may be altered during chemotherapy.[15]

Understanding the bidirectional communication between drugs and the gut microbiome may open new perspectives for more effective pharmacological treatment of health conditions. Most papers describing pharmacomicrobiomics have focused on antibiotics, proton pump inhibitors, and metformin. There is also a bunch of evidence pointing to the interaction between psychotropic drugs and the microbiome.[16,17] Nevertheless, recent data indicate that bidirectional interactions between some chemotherapeutic agents and the gut microbiome may affect the response and efficiency of anti-cancer treatment.[18] Therefore, in the present review, we mainly concentrate on three main aspects: (1) interaction between the most significant cell-cycle specific anti-cancer drugs (Figure 1) and gut microbiome, (2) mapping of drug metabolism by gut microbiome, and (3) limitations and future perspectives by mentioning key points with their specialist's justifications and presenting trials that are under investigation.

Anti-metabolites specific for S phase

5-fluorouracil (5-FU)

5-FU (chemical formula: $C_4H_3FN_2O_2$) is used as a chemotherapeutic agent for drugs specific to the S phase of the cell cycle. The side effects of 5-FU include hemorrhagic enteritis and both neurological and hematological toxicity.[19] 5-FU-induced intestinal mucositis can be reduced by probiotic administration, *Streptococcus thermophilus* ST4, which has been observed in animal model studies.[20] The efficiency of 5-FU is limited by its basic properties, such as short half-life (bolus intravenous – 10–15 min), rapid metabolism, and low bioavailability.[21,22] 5-FU is metabolized into its inactive metabolite dihydrofluorouracil by Proteobacteria and Firmicutes.[23] Recently, Wan *et al.* investigated the interaction between chemotherapeutic drugs (5-FU – cell-cycle specific drug and oxaliplatin – cell-cycle nonspecific drug) and the gut microbiome during chemotherapy.[24] It is noteworthy that the gut microbiome was analyzed by two different methods, that is, 16S rRNA sequencing and shotgun metagenomic sequencing, the latter providing a functional point of view. Based on 16S rRNA sequencing, 5-FU administration decreased the counts of *Streptococcus* and *Bacteroides* genera and increased *Clostridium hathewayi* and Lachnospiraceae abundance. Meanwhile, oxaliplatin was related to the depletion of the Lachnospiraceae family with an increase in *Lactobacillus* and *Streptococcus* genera. The results of shotgun metagenomic sequencing showed significant enrichment of *Streptococcus salivarius* and *Ligilactobacillus salivarius* after chemotherapy. Additionally, it was demonstrated that the alterations of metabolism in the 5-FU group suggest that gut microbiota can provide NAD^+ - nicotinamide

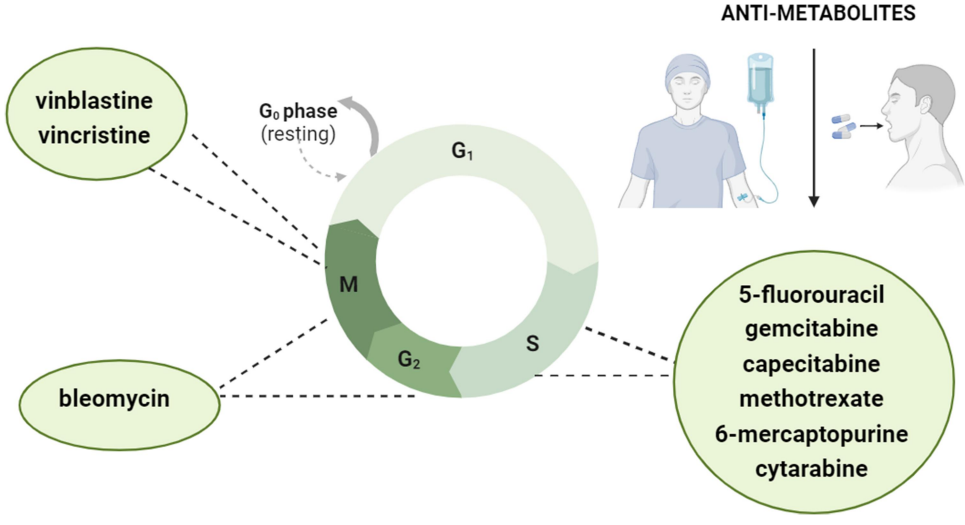

Figure 1. The most significant cell-cycle specific drugs used in anti-cancer therapy. Own elaboration based on literature. This figure was created using Biorender.com.

adenine dinucleotide to inhibit cancer cell autophagy.[24] Since, a response to chemotherapy can be affected by bidirectional interactions between the gut microbiome and drugs[24,25]; an intra-tumoral microenvironment may also play a significant role in this context. The assessment 'tumor microenvironment' is used in terms of both groups of cells, i.e. cancer cells and types of cells (such as immune cells, blood vessels, fibroblasts, mediators – enzymes, cytokines) which surround them.[26] Notably, tumor tissues include also bacteria, fungi, viruses, and archaea which overall is assessed as intratumor microbiota.[26] Nejman et al. reported that each tumor type presents a distinct composition of microbiome.[27] Some studies refer to breast cancer due to the fact that the abundance of microbes building microbiome in this tumor is particularly rich.[27,28] Moreover, it was demonstrated that microbial signature is different considering a particular type of breast cancer, i.e. hormone receptor-positive breast cancer and hormone receptor-negative breast cancer.[29] *Escherichia coli*, which is a member of the intratumoral microbiota of colorectal cancer tissue, is resistant to 5-FU.[30] The most dominant bacterium in colorectal cancer tissue is *Fusobacterium nucleatum*.[30] The modification of response to chemotherapy by *F. nucleatum* was analyzed in a study by Yu *et al*. study.[31] It was noted that *F. nucleatum* modulates autophagy, thus promoting resistance to chemotherapy in colorectal cancer. Another study reported that the enhancement of resistance to chemotherapy in colorectal cancer is associated with the ability of *F. nucleatum* to upregulate the expression of BIRC3 (cellular IAP2 – inhibitors of apoptosis protein).[32] Therefore, the measurement of *F. nucleatum* in both stool and cancer tissue seems to be significant in the effective management of colorectal cancer.[31] The association between chemosensitivity and modulation of microbiome has also been investigated in colorectal cancer cell lines (HT-29 and HCT-116).[33] In that study, it was demonstrated that the treatment with *Lactobacillus plantarum* supernatant and chemotherapy based on 5-FU caused cell death through the indication of caspase-3 activity; moreover, the inactivation of Wnt/β-catenin signaling of chemoresistant colorectal cancer cells was noted. Therefore, this combination (*L. plantarum* supernatant and 5-FU) can increases the chemosensitivity in colorectal cancer cells.[33] Similar results were obtained in another study conducting on 5-FU-resistant colorectal cancer cells HCT-116 in which it was shown that *L. plantarum* can act as a chemosensitizer.[34]

5-FU causes not only dysbiotic changes in the gut microbiome but also in the oral microbiome, resulting in the development of oral mucositis, which is one of the most common side effects of chemotherapy.[35] In a study by Hong *et al*., it was shown that *F. nucleatum* and *Prevotella oris* are enriched during mucositis.[35] The pathogenic factors of *P. oris* origin include immunoglobulin A protease, hyaluronidase, and β-lactamase.[36] Notably, *P. oris* is a gram-negative and anaerobic periodontopathogen that can interact with the major periodontopathic bacterium *Porphyromonas gingivalis* with numerous virulence factors (mainly gingipains, fimbriae, lipopolysaccharide, outer membrane vesicles, nucleoside diphosphate kinase, and serine phosphatase) belonging to the red complex group of bacteria.[36,37] *P. gingivalis* co-aggregates with *F. nucleatum*, a pathogen also involved in the development of periodontal diseases.[36,37]

The efficiency of chemotherapy may be affected by some metabolites that produce the gut microbiota. Urolithin A is a natural metabolite of ellagitannins, which is a dietary polyphenols.[38–40] Gut microbiome affects the transformation of ellagitannins into urolithin A; however, its bioavailability depends on the individual's gut microbiome composition.[39,40] This metabolite is characterized by immunomodulatory properties with anti-inflammatory activity.[41] Ghosh *et al*. have reported that urolithin A and UAS03 (its structural analog) chemosensitized colon cancer resistant to 5-FU.[42] Therefore, it is worth considering the consumption of urolithin A during 5-FU-based chemotherapy.[42]

The gut-microbiota-brain axis has been shown to be involved in the pathogenesis of depression.[43] In a study by Zhang *et al*. ($n = 20$ males, 5-week-old Sprague-Dawley rats; $n = 10$ – control group, $n = 10$–5-FU treatment group), the link between gut

microbiome changes caused by 5-FU and depressive mood was investigated.[44] The gut microbiome was analyzed with 16S rRNA sequencing. Depressive-like behavior was assessed using specific behavioral tests. It was observed that the development of depressive-like behaviors and prefrontal cortex disorders might have been induced by 5-FU and related to gut microbiome alterations following drug use.[44] Neuroscientific evidence confirms that prefrontal cortex is involved in depression. The alterations of prefrontal cortex metabolic can be caused by 5-FU and that mechanism is based on the functioning of microbiome-gut-brain axis.[44] 5-FU changed both the abundance and diversity of the gut microbiome. Moreover, depressive-like behaviors and prefrontal cortex disorders were alleviated by fecal microbiota transplantation (FMT) from healthy controls in rats receiving 5-FU.[44] Consequently, these results confirm that 5-FU-induced depressive-like behaviors are strongly associated with the gut microbiome, and an appropriate modification can relieve these symptoms.

Gemcitabine

Gemcitabine is a pyrimidine nucleoside analog that acts as an anti-cancer drug.[45] Currently, gemcitabine remains the cornerstone in the treatment of pancreatic cancer.[46,47] The intra-tumoral microenvironment in the case of pancreatic cancer may play a significant role in the efficacy of gemcitabine-based chemotherapy (Figure 2).

Because the tumor microenvironment mediates the efficacy of gemcitabine-based chemotherapy, the question arises as to whether the elimination of microbes residing in the tumor can alter the response to that treatment. Kang *et al.* used dual-

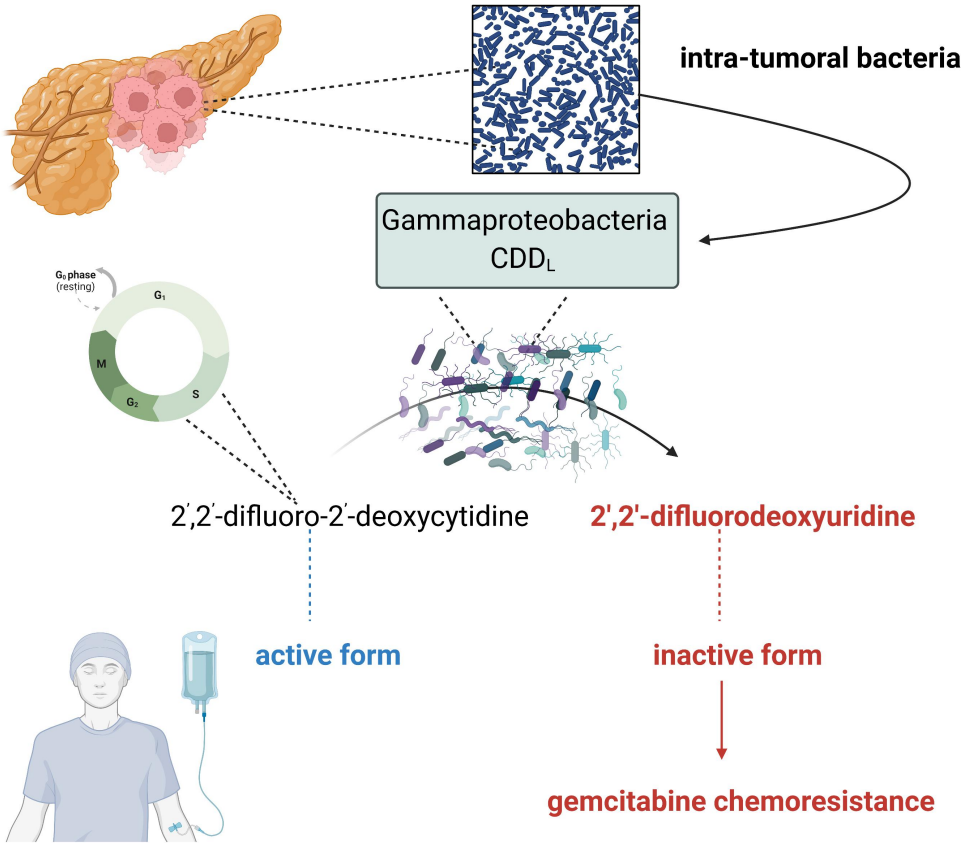

Figure 2. Gemcitabine (2′,2′-difluoro-2′-deoxycytidine) is widely used as a chemotherapeutic agent to treat pancreatic cancer. Currently, it is known that tumours are not sterile and intra-tumoral microbes communities exist. Moreover, some bacterium may affect the efficiency of gemcitabine-based chemotherapy. In that context, Gammaproteobacteria is extremely significant which is commonly found in PDAC (pancreatic ductal adenocarcinoma) tumour tissues. Long isoform of bacterial enzyme cytidine deaminase (CDD$_L$) is seen in Gammaproteobacteria. It causes 2′,2′-difluoro-2′-deoxycytidine transformation into its inactivated form, i.e. 2′,2′-difluorodeoxyuridine consequently leading to gemcitabine chemoresistance. Own elaboration based on literature.[6,48–50] this figure was created using Biorender.com.

cascade responsive nanoparticles (sNP@G/IR) with the ability to kill intra-tumoral bacteria and control the release of chemotherapeutic agents was used.[51] It included hyaluronic acid shell and glutathione-responsive polymer-core that encapsulates gemcitabine and a photothermal agent. It has been reported that the elimination of intracellular bacteria residing in tumors improves anticancer treatment to a large extent.[51]

Gemcitabine alters gut microbiota, which has been shown in pancreatic cancer xenograft mice receiving this drug for 3 weeks.[52] Gemcitabine reduces the proportion of gram-positive bacteria Firmicutes and Gram-negative Bacteroidetes.[52] Microbiota-derived metabolites are also involved in bidirectional interactions between gemcitabine and the gut microbiome. Butyrate (C4), which is a microbial metabolite, provides multiple benefits, such as improvement of intestinal barrier integrity, upregulation of mucin-2 (*MUC*2) gene expression, inhibition of pro-inflammatory mediators, and others.[53] Panebianco et al. investigated the effect of sodium butyrate on response to gemcitabine in both *in vitro* and *in vivo* models.[54] It was shown that butyrate acts by slowing proliferation and promoting apoptosis in human pancreatic cell lines, leading to enhancement of gemcitabine efficiency. In a pancreatic cancer mouse model, the agent enhanced intestinal integrity and modulated the composition of microbiota by increasing the counts of SCFAs bacterial producers.[54]

Lipopolysaccharide (LPS) originates from gram-negative bacteria, because it is a major component of their outer membrane.[55] It can be considered as a negative predictor for the efficacy of adjuvant gemcitabine in the case of PDAC.[56] Recently, it was also shown that LPS can stimulate the growth of breast tumors, which include mainly gram-negative bacteria.[57] It was elegantly summarized that such an event might be due to the following mechanisms: (1) the treatment of breast cancer cells using LPS increases S100A7 expression in these cells *in vitro*; (2) the overexpression of S100A7 downregulates Toll-like receptor 4 (TLR4) whereas upregulates the expression of advanced glycation end product receptor (RAGE) in breast cancer cells; and (3) the novel signaling axis LPS/S100A7/TLR4/RAGE can be involved in the enhancement of tumor growth.[57] Considering breast cancer and microbiome aspects, it should be emphasized that there is a difference in bacterial profile in breast tissue in healthy subjects and breast cancer patients.[58] Moreover, both local and gut microbial imbalance known commonly as dysbiosis are observed in these patients.[59,60] The colonization of breast cancer by *F. nucleatum* stimulates the growing of tumor as well as progress metastasis.[61] In Barroso-Sousa et al. phase II study, it was analyzed whether pembrolizumab in combination with palliative radiation therapy affects the outcome of patients with hormone receptor-positive metastatic breast cancer.[62] Pembrolizumab was given intravenously in dose 200 mg 2–7 d prior to radiation (5 treatment, 4 Gy) and on day 1 of repeating 21-d cycles. It was noted that the administration of pembrolizumab together with radiation treatment did not provide an objective response in these patients.[62]

Capecitabine

Capecitabine is an oral pro-drug of fluorouracil.[63,64] The interaction between the gut microbiome and capecitabine was analyzed in a study comprising 33 patients with metastatic colorectal cancer patients.[63] Stool samples were collected before, during, and after three cycles of capecitabine. The gut microbiome was analyzed using 16S rRNA sequencing. The gut microbiome was not significantly affected by the three cycles of capecitabine. Moreover, microbial diversity and bacterial abundance were not significantly different between responders and non-responders.[63] However, in another study, it was noted that CapeOx (capecitabine plus oxaliplatin) therapy significantly alters gut microbiota of colorectal cancer patients (treated with radical surgery and above mentioned adjuvant therapy).[65] Also, in Kaźmierczak-Siedlecka *et al.* study, it was shown that the proportion between SCFAs is changed in colorectal cancer patients in preoperative period.[66] Recently, in 2023

Ziemons *et al.* investigated the impact of three cycles of capecitabine (± bevacizumab, $n = 32$) on both SCFAs and branched chain fatty acids (BCFAs) measured from fecal samples in patients ($n = 44$) with metastatic or unresectable colorectal cancer.[67] A significant decrease of valerate and caproate during three cycles of capecitabine was observed. There was no significant association between SCFAs/BCFAs and nutritional status, chemotherapy-related toxicity, or physical performance.[67] However, the modulation of gut microbiome by supplementation of probiotic *Lactobacillus rhamnosus* R0011 improved the efficacy of capecitabine-based chemotherapy, which has been recently shown in an animal model (male Balb/c mice, colon cancer) study.[68] The impact of prebiotics (xylo-oligosaccharides) on gut microbiota, side effects, and drug (capecitabine) bioavailability in the case of colorectal cancer patients is under investigation.[69] In Guan *et al.* study including human epidermal growth factor receptor 2 (HER-2) negative metastatic breast cancer patients, it was observed that composition, diversity, and functional structure of gut microbiome were different in participants treated with metronomic chemotherapy (capecitabine) compared to the conventional dose of chemotherapy.[64] The different results obtained from the above-mentioned studies may be associated with the following potential reasons: (1) the impact of capecitabine on gut microbiome can be determined by its dose, (2) capecitabine can interact with gut microbiome and vice versa depending on type of cancers (i.e. gastrointestinal cancers vs. hormone-dependent tumors) involving possible other underlying mechanisms, (3) gut microbiota alterations can depend on the combination of chemotherapeutic drugs. Interestingly, in published study protocol the role of intestinal microbiota in the treatment (regarding capecitabine and TAS-102) of cancer as a part of personalized medicine has also been highlighted.[70]

Methotrexate

Methotrexate (4-amino-4-deoxy-N-10-methylpteroyl glutamic acid) is a folic acid antagonist.[71,72] At high doses, it inhibits DNA synthesis, repair, and cellular replication.[71,73] Methotrexate is used to treat cancer and autoimmune diseases (for instance rheumatoid arthritis) owing to its immunosuppressive function.[74,75] Clinical response to methotrexate can be affected by the gut microbiome.[76] Additionally, side effects of methotrexate, including gastrointestinal toxicity, might limit its efficacy. In a mouse model study, it was observed that methotrexate caused hepatotoxicity and altered the gut microbiome by increasing *Aerococcus*, *Collinsella*, *Staphylococcus*, *Enterococcus*, *Streptococcus* while reducing the levels of *Lactobacillus*, *Bifidobacterium*, *Ruminococcus*, *norank_f_Muribaculaceae*, *unclassified_f_Lachnospiraceae*, *norank_f_Lachnospiraceae*, *Eubacterium_xylanophilum_group*, *Phascolarctobacterium*, and *Faecalibaculum*.[77] Nevertheless, only some of these microbes (*Streptococcus*, *Enterococcus*, *Staphylococcus*, *Collinsella*, *Phascolarctobacterium*, *Faecalibaculum*, *norank_f_Muribaculaceae*) were related to liver injury.[77] In the reduction of methotrexate-related intestinal toxicity, Toll-like receptor 2 (TLR2) is involved.[78,79] In a Huang *et al.* study it was observed that methotrexate-induced intestinal toxicity can be reduced by leucovorin (folinic acid) via modulation of gut microbiome.[74] Lethal intestinal injury after treatment with high-dose of methotrexate can be alleviated by dietary restrictions, which have been shown in animal model study.[71] Short-term dietary restrictions altered gut microbiome by significantly increasing the level of *Lactobacillus* genus.[71] Ferreira *et al.* assessed whether vitamins C and B_2 can reduce methotrexate associated with gastrointestinal mucositis.[80] It was noted that *in vitro* these vitamins increase the growth of *Blautia coccoides* as well as *Roseburia intestinalis*, thus they can change the composition of gut microbiota, but their impact on methotrexate-induced mucositis is limited.[80] FMT is the most modern method applied to modify gut microbiome; nevertheless, it is still approved only for the treatment of recurrent *Clostridioides difficile* infection.[81,82] Wardill *et al.* reported that modulation of gut microbiome by FMT after methotrexate treatment has no significant influence on gastrointestinal toxicity.[83] Nevertheless, the administration of antibiotics prior to chemotherapy aggravated that toxicity by impairment of mucosal recovery ($p < 0.0001$), increase of severity of diarrhea ($p = 0.0007$) and mortality

associated with treatment ($p = 0.0045$). Moreover, restoring the gut microbiome by autologous FMT reversed these effects.[83]

6-mercaptopurine

6-mercaptopurine is an antiproliferative purine analog and a metabolite of azathioprine. It is not only used to treat inflammatory bowel diseases, non-Hodgkin lymphoma, and lymphoblastic leukemia, but it also has therapeutic potential in solid tumor management.[84–87] 6-mercaptopurine is characterized by its low bioavailability (16%), short half-life (0.5–1.5 h), and high first-pass effect.[84] It is a part of thiopurine metabolic pathway. At the beginning, azathioprine is cleaved to 6-mercaptopurine; next, there are three metabolic pathways in 6-mercaptopurine metabolism, that is, (1) inactive 6-thiouric acid (enzyme – xanthine oxidase), (2) inactive 6-methylmercaptopurine (enzyme – thiopurine methyltransferase), and (3) therapeutic 6-thioguanine nucleotide (enzyme – hypoxanthine phosphoribosyl transferase).[88] Oancea et al. reported that an alternative way of thioguanine pro-drug conversion is through bacteria.[89] Recently, in a rat model study, it was shown that the pharmacokinetics of the above-mentioned metabolites of azathioprine (i.e., both 6-thioguanine nucleotide and 6-methylmercaptopurine) is altered by gut microbial metabolism.[90] Moreover, the efficacy of azathioprine is affected by the synthesis of microbial butyrate, which has been observed in patients with inflammatory bowel diseases.[91]

Antibiotics specific for G_2/M phase

Bleomycin

Bleomycin is a broad-spectrum anticancer drug belonging to the subfamily of glycopeptide antibiotics.[92,93] The side effects of bleomycin include lung injury. Bleomycin-induced pulmonary fibrosis has been considered in the context of the gut-lung axis.[94] The gut microbiota imbalance was observed in a mouse model with pulmonary fibrosis induced by bleomycin; the amounts of *Catenibacterium*, *Lactobacillus* – *L. johnsonii* and *L. gasseri* were decreased, whereas the abundance of *Verrucomicrobiales* and *Enterobacteriales* was increased.[94] Notably, both *Catenibacterium* and *Lactobacillus* are probiotics, thus they provide beneficial effects.[95,96] The role of gut microbiota and gut-lung axis in case of bleomycin-induced lung injury has also been investigated in Yoon *et al.* mice model study.[97] It was shown that the role of gut microbiota is mostly important in acute phase of bleomycin treatment.[97] Bleomycin-induced pulmonary fibrosis can be beneficially affected by phycocyanin, which has been shown in C57BL/6 mice model study.[98] It was noted that phycocyanin not only reduces the pro-inflammatory cytokines but also significantly increases both bacterial diversity and SCFAs-bacterial producers as well as decreases inflammation-related bacteria.[98] Phycocyanin belongs to the phycobiliprotein family. It is obtained from different species including *Spirulina* sp., *Phormidium* sp., *Synechococcus* sp., and others.[99] Phycocyanin is characterized by anti-tumor properties; therefore, it can be considered as an anti-cancer agent.[99] Huang *et al.* reported that phycocyanin suppresses epithelial-mesenchymal transition and affects the Akt/β-catenin pathway, thus inhibiting pancreatic cancer metastasis.[100]

Although the interactions between bleomycin and the gut microbiome are not fully described and currently most of the presented studies are conducted using animal models, there are promising opportunities to consider bleomycin-related pharmacomicrobiomics in oncology.

Drugs specific for M phase

Vinblastine and vincristine

Vinblastine and vincristine are monoterpene indole alkaloids (MIAs) of Catharanthus (or Vinca)[101] origin, also produced using genetic engineering techniques.[102] Both of which have proven efficacy in cancer treatment mainly due to mitotic arrest and/or cell death.[103–105] Information on the interaction between these agents and the microbiome is scarce. In a study by Rtibi *et al.*[106], it was

demonstrated that vinblastine administered to rats diminished the gastrointestinal motility (12.88% compared to vehicle and 24.33% compared to loperamide) and consequently induced constipation (11.16% compared to vehicle and 32.95% compared to loperamide). This proves that the interaction with the microbiome as gut microbes regulate the motility predominantly via their cell wall components bioactive products of their metabolism[107,108] and the constipation was proved to be related to gut microbiota alterations.[109] These changes were accompanied by alterations in pro- and antioxidant synthesis, which also negatively influenced lipid peroxidation. Again, both were linked to gut microbiota.[110] Also, a clinical trial in 2011[111] found that the administration of high-dose methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) with or without granulocyte colony-stimulating factor resulted in a relatively high percentage of nausea and/or vomiting. These results suggest, although not directly, that vinblastine has the potential to alter the microbiological niche within the gut, especially as such functional phenotypes are linked to microbiota-gut-brain axis dysregulation.[112] Nevertheless, more studies with vinblastine administered alone are needed to verify this hypothesis. In addition, it was historically verified that the administration of peritumoral hyaluronidase may prevent vinblastine-induced local inflammation and simultaneously as a pretreatment can drastically increase the activity of low-dose vinblastine.[113,114] One might conclude that the gut microbiota functions might be at least partly responsible for the action of vinblastine. Indeed, hyaluronidases might be of microbiota-origin.[115]

A study by Peiris and Oppenheim[116] found that the antimicrobial activity of vincristine was minimal. However, as elegantly demonstrated by López-Gómez[117] a 10-d administration of vincristine resulted in gastrointestinal motility inhibition and alterations in the digestive wall in the ileum and colon, including villus shortening and inflammatory nodules, respectively. Some of these results were replicated recently.[118,119] In the latter one[119], a cannabinoid antagonist was found to counteract dysmotility. As evidenced in the literature, both the structure of the gut[120], its motility[107,108] and inflammatory processes taking place there are predominantly driven by microorganisms.[121] In addition, gut microbiota structure and functions might shape the response to vincristine. Taper *et al.* tested the effect of administering inulin or oligofructose to mice with transplantable liver tumors treated with, inter alia, vincristine, and observed a potentiation of anti-carcinogenic effects, confirming that gut microbiota might be an object of interest in anti-tumor therapy.[122]

Other anti-cancer drugs

Platinum-based drugs

Cisplatin, carboplatin, and oxaliplatin belong to the platinum-based chemotherapeutic which are widely used in oncology.[123] There are two mechanisms by which cisplatin acts. First one regards cellular uptake, DNA platination and activation of cellular process leading to apoptosis of cancer cells.[123,124] Second mechanism is an alternative effect and it includes short acidification of cytoplasm, disruption of RNA transcription, inhibition of oncogenic proteins and alterations of tumor cells metabolic plasticity.[123] Gui et al. in lung cancer mice model study reported that the response to anti-cancer treatment based on cisplatin can be modulate by commensal microbiota.[125] It was shown that co-treatment with probiotics – *Lactobacillus acidophilus* affects the expressions of interferon-γ (IFN-γ), GZMB, PRF1 in CD8+ T cells which were previously decreased by administration of antibiotics (such as vancomycin, ampicillin, neomycin). Additionally, the improvement of survival rate was observed in mice treated with cisplatin and *L. acidophilus* ($p = 0.048$) in contrast to mice which received cisplatin and above listed antibiotics.[125] The enhancement of anti-tumor effects of chemotherapeutic cisplatin (in combination with gemcitabine) through administration of probiotics (*Lactobacillus casei* Shirota and *Bifidobacterium breve*) has also been recently confirmed in urothelial cancer in Miyake et al. study.[126] On the other hand, as we previously concerned, some of microbes may enhance chemoresistance. In Liang et al. study it was shown

that *F. nucleatum* promotes cisplatin resistance in case of esophageal squamous cell carcinoma.[127] It is based on the ability of *F. nucleatum* to induction of myeloid-derived suppressor cells by the activation of NOD-like receptor protein 3 (NLRP3).[127]

Paclitaxel

Paclitaxel is a class of taxanes, and it has an impact on the stabilization of microtubules. It is used as a first-line drug in breast cancer patients.[128] It is also used to treat other type of cancers, such as non-small cell lung cancer. Paclitaxel affects microbiome causing dysbiotic alterations.[129] Interestingly, some of gut microbial imbalance caused by other disease than cancer can influence the response to paclitaxel, which has been shown in Kesh et al. study.[130] They reported that microbiome dysbiosis caused by type 2 diabetes can be associated with chemoresistance (paclitaxel, gemcitabine) in case of pancreatic adenocarcinoma.[130]

Doxorubicin

Doxorubicin is an anti-cancer agent which induces cancer cell death through many intracellular target inhibition of topoisomerase II or generation of reactive oxygen species.[131] It belongs to the nonselective class I anthracycline family.[132] The bidirectional interactions between doxorubicin and gut microbiome were investigated in Bawaneh et al. study regarding triple-negative breast cancer (female BALB/c mice).[131] Intestinal microbiota was analyzed from fecal samples. It was noted that doxorubicin was associated with increased abundance of *A. muciniphila*; moreover, doxorubicin responders present an elevated abundance of this bacterium prior to this treatment.[133] The results of another study show that neoadjuvant chemotherapy affects breast tumor microbiota.[134] Interestingly, doxorubicin can be inactivated by *Raoultella planticola* via reductive deglycosylation; moreover, doxorubicin may be metabolized into inactive metabolites by *Klebsiella pneumoniae* and *Escherichia coli* BW25113.[132,135]

Mapping of drug metabolism by gut microbiome

Mapping of microbiota-host-drug networks can be a part of personalized medicine.[136–139] This is based on the assumption that biotransformation involves microbes chemically transforming drugs.[140] It should be emphasized that bacterial metabolism regarding both reduction and hydrolysis results in the generation of nonpolar compounds. Low molecular weight byproducts; therefore, this metabolism is different from liver metabolism, which is mainly based on oxidation and conjugation.[141] Nevertheless, some drugs have minimal contact with intestinal bacteria because they are absorbed in the upper gut.[141] Javdan *et al.* reported that personalized microbiomes metabolize drugs in different ways; thus, the interactions between drugs and gut microbiome vary between individuals and, consequently, can be considered as personalized medicine.[137] It is also related to the ways of drug administration, that is, oral, sublingual, parenteral. Some of drugs are taken sublingually to avoid first-pass liver metabolism and achieve high bioavailability and rapid effects.[142] For instance, oral administration of nitroglycerin provides approximately 10–20% of its bioavailability; thus, sublingual administration is recommended to provide rapid effects in case of angina pectoris.[143] Zimmermann et al. have reported that many of oral drugs are modified by microorganisms.[144] They measured the ability of 76 diverse human gut bacteria to metabolize 271 oral drugs. Both the systemic and intestinal metabolism of drugs in mice can be influenced by the microbiome (more precisely by microbiome-encoded enzymes). These results indicate that the genomic content of gut bacteria is strongly associated with alterations in drug metabolism.[144] In another study, 70 interactions between bacteria and drugs were reported.[140] It is noteworthy that some of these interactions were observed by the ability of bacteria to store drugs intracellularly; however, without chemical transformation.[140] Therefore, these results indicate the underlying mechanism of this mapping, which regards not only the biotransformation of drugs by microorganisms

but also the bioaccumulation of drugs by bacteria.

Perspectives for the future and limitations

Key points:

- It is recommended to analyze the influence of cell-cycle specific anti-cancer drugs in combination with cell-cycle phase-nonspecific anti-tumor agents or monoclonal antibodies on the gut microbiome and vice versa.

Justification: Combinations of drugs such as 5-FU + oxaliplatin, capecitabine + bevacizumab, CapeOx (capecitabine + oxaliplatin), and others are used. The different results of the interaction between monotherapy vs. gut microbiome compared to a mixture of anti-tumor agents vs. gut microbiome can be observed. Moreover, monoclonal antibodies, such as bevacizumab, act against vascular endothelial growth factor[145] therefore, it presents another mechanism of action.

- It is recommended to take into consideration factors which modulate the gut microbiome.

Justification: The gut microbiome is modulated by multiple factors, such as diet and administration of prebiotics, probiotics, synbiotics (prebiotics and probiotics), and postbiotics. Therefore, observation during cycles of chemotherapy should also consider additional factors that may affect the interactions between drugs and microbes.

- Individual matching of therapeutic gut microbiome modulators can beneficially affect the restoration of gut microbiome imbalance and, consequently, enhance the efficiency of anti-cancer treatment.

Justification: The modification of the gut microbiome through therapeutic methods, such as administration of prebiotics, probiotics, synbiotics, postbiotics, and FMT, can restore gut microbiome imbalance; however, the introduction of these methods should be based not only on underlying disease but also on additional disorders/conditions as well as drug administration and their interactions.

- The interactions between drugs and the gut microbiome should consider not only bacteria but also other components of that community.

Justification: The gut microbiome should be considered a complex community of bacteria, fungi, viruses, archaea, and parasites.[146] It would be interesting to analyze the interactions between drugs and fungi. For instance, the fungal probiotic *Saccharomyces boulardii* CNCM I-745 is resistant to antibiotics because of its natural fungal properties.[147]

- The way of drug administration may affect their interactions with gut microbiome.

Justification: Drugs that are absorbed in the upper part of the gastrointestinal tract exhibit decreased interactions with gut microbes.

Although the impact of the microbiome on the response to chemotherapeutics seems to be clinically significant, there are a limited number of clinical trials that directly analyze its relationship. All the related studies revealed in "Clinicaltrials.gov, clinicaltrialsregister.eu, eortc.org/clinical-trials-database, trialsearch.who.int" are shown in Table 1. In the future, new prospective clinical trials should be conducted in this field. There is a need for studies investigating the changes in the microbiome before and after chemotherapeutic treatment. Therefore, the potential of changing the microbiota composition before treatment to obtain a better response should be investigated.

Conclusions

Currently, pharmacomicrobiomics is a hot topic that opens new perspectives in personalized cancer management. It is extremely necessary due to the fact that the range of problems affecting oncological patients is wide, that is, from the early stage of

Table 1. The summary of chemotherapeutics which are under investigation based on available clinical trial databases.

Chemotherapeutics	ID	Official Title	Status	Description	Source
5-fluorouracil Leucovorin Oxaliplatin	NCT03698461	Comparative Analysis of Immune Profile Following Neoadjuvant Chemotherapy in Colorectal Liver Metastases (CRLM): A Prospective Pilot Clinical Trial	Active, not recruiting, Phase 2	Although the study does not focus on the microbiome specifically, the assessment of the microbiome profile in stool samples through whole metagenomic sequencing is included. According to provided description, patients will be treated with bevacizumab and atezolizumab in combination with FOLFOX. The microbiome will be measured on day 1 before the first atezolizumab and 15 days after treatment and at time of hepatic metastasectomy or liver biopsy after 6 cycles of treatment (each cycle is 14 d).	https://clinicaltrials.gov/study/NCT03698461?term=Microbiome%20&intr=5-Fluorouracil&rank=1, accessed: 2023.07.09
5-fluorouracil Liposomal irinotecan Leucovorin Carboplatin Capecitabine	NCT03764553	Liposomal iRInotecan, Carboplatin or oXaliplatin in the First-Line Treatment of Esophagogastric Cancer: Randomized Phase 2 Study	Recruiting, Phase 2	Although the study does not focus on the microbiome specifically, the assessment of the microbiome profile in fecal samples as the potential biomarkers for response to treatment and toxicity is one of the outcome measures. The study aims to compare the treatment with Liposomal Irinotecan + leucovorin + 5-fluorouracil as the first arm and carboplatin +capecitabine (second arm) and capecitabine +oxaliplatin (third arm).	https://clinicaltrials.gov/study/NCT03764553?term=Microbiome%20&intr=5-Fluorouracil&rank=2, accessed: 2023.07.09
FOLFIRINOX: 5-fluorouracil Leucovorin Irinotecan Oxaliplatin	NCT05462496	Pilot Study of Gut Microbiome Modulation to Enable Efficacy of Neoadjuvant Checkpoint-based Immunotherapy Following Chemotherapy in Pancreatic Adenocarcinoma	Not yet recruiting, Phase 2	The study aims to assess the immune activation in pancreatic cancer after treatment with antibiotics and pembrolizumab and the safety of this combination. In this clinical trial, the correlation of immune changes with microbiome abundance and composition will be assessed. Around 25 patients will be treated with FOLFIRINOX, then with antibiotics and metronidazole, and finally with pembrolizumab. In the end, surgical resection of tumor will be performed.	https://clinicaltrials.gov/study/NCT05462496?term=Microbiome%20&intr=5-Fluorouracil&rank=4, accessed: 2023.07.09
Capecitabine Oxaliplatin	NCT05177133	Anti-PD-1, Capecitabine, and Oxaliplatin for the First-line Treatment of dMMR Esophagogastric Cancer (AuspiCiOus-dMMR): a Proof-of-principle Study	Recruiting, Phase 2	The 25 patients will be treated with Capecitabine, oxaliplatin, and retifanlimab (anti-PD-1). One of the outcome measures is a change in the composition of the fecal microbiome with the use of DNA sequencing as a potential biomarker for response to treatment.	https://clinicaltrials.gov/study/NCT05177133?term=Microbiome%20and%20capecitabine&rank=4, accessed: 2023.07.09
Cisplatin Gemcitabine	ISRCTN11210442	Exploring the microbiome in patients with advanced biliary tract cancer in a first-line study of durvalumab (MEDI4736) in combination with cisplatin/gemcitabine	Ongoing	The study will investigate the population of around 70 patients baseline alpha diversity from patients who responded and not responded to therapy (cisplatin, gemcitabine, and durvalumab), trying to identify its predictive role.	https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN11210442, accessed: 2023.07.09
XELOX: Oxaliplatin Capecitabine	ChiCTR2100046237	Effects of prebiotic supplement on gut microbiota, drug bioavailability, and adverse effects in patients with colorectal cancer at different primary tumor locations receiving chemotherapy: study protocol for a randomized clinical trial	Recruiting, Interventional study	50 Participants will be divided into two arms and randomly allocated to the prebiotic group ($n = 25$) and control group ($n = 25$). The study will assess the potential of gut microbiota modification in the improvement of the efficacy of chemotherapy in colorectal cancer as well as in reducing the number of adverse events.	https://www.chictr.org.cn/showprojEN.html?proj=126462 accessed: 2023.07.11

(*Continued*)

Table 1. (Continued).

Chemotherapeutics	ID	Official Title	Status	Description	Source
mFOLFIRINOX: 5-fluorouracil Leucovorin Irinotecan Oxaliplatin Or Gemcitabine + nab-paclitaxel	ACTRN12619000409178	AGITG MASTERPLAN: a randomized phase II study of modified FOLFIRINOX alone or in combination with stereotactic body radiotherapy for patients with high-risk and locally advanced pancreatic cancer	Recruiting, Phase II	The study will compare the efficacy of modified FOLFIRINOX alone or in combination with stereotactic body radiotherapy for 120 patients with pancreatic cancer. Microbiome samples will be evaluated as potential prognostic/predictive biomarkers and the correlation of them with clinical endpoints will be analyzed.	[148] https://www.australianclinicaltrials.gov.au/anzctr/trial/ACTRN12619000409178 accessed: 2023.07.11

cancer with no metastasis (with different responses to the treatment) to non-resectable tumors with multiple metastases. Among others, the transformation of chemotherapeutic drugs into their inactive form by specific microbes and the consequent promotion of chemoresistance confirms that pharmacomicrobiomics should be included in personalized medicine. Despite the fact that this paper is concentrated on cell-cycle specific anti-cancer drugs, it should be mentioned that immune checkpoint inhibitors and overall immunotherapy are strongly involved into bidirectional interactions between them and microbiome. Some of the bacteria, such as *A. muciniphila*, is able to enhance CTLA-4 as well as PD-1/PD-L1 blockade thus it improves the effects of immunotherapy. The chemical structure of drugs, pharmacodynamics, pharmacokinetics, drug-drug and drug-nutrient interactions, tumor microenvironment, composition of the gut microbiome, and metabolome must be considered. Thus, it is recommended that studies assessing pharmacomicrobiomics be designed and conducted by a multidisciplinary team of specialists, such as oncologists, oncological surgeons, biotechnologists, pharmacists, and nutritionists.

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