


Clinical Implications of Gut-Lung Axis in Systemic Chemotherapy for Lung Cancer

Indry Agatha Rihi Pake[1], Widiya Hari Kurnia[2], Mirna Nastiti Louqi Machfud[3], Stella Pangestika[4], Candra Muhammad Yusuf Hidayatullah[5], Arya Marganda Simanjuntak[6,7]

[1]T.C.Hillers Regional Public Hospital, Flores, East Nusa Tenggara, [2]Internship, dr. Suyudi General Hospital, Lamongan, East Java, [3]Ngudi Waluyo Wlingi Regional Public Hospital, Blitar, East Java, [4]Batara Guru Public Hospital, South Sulawesi, [5]Bonang 2 Public Health Department, [6]Research Assistant, Pulmonary and Critical Medicine Division, Department of Internal Medicine, Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital, Pekanbaru, Riau, [7]Clinical Clerkship, Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital, Pekanbaru, Riau, Indonesia

ABSTRACT

Lung cancer incidence continues to increase globally, with an estimated mortality rate of 18% worldwide. Current management strategies focus on early screening, early treatment, and palliative care. However, more fundamental approaches are needed to improve treatment outcomes. The gut-lung axis has emerged as an important factor in lung cancer pathophysiology, as it plays a role in pulmonary immune defense and is influenced by changes in gut and lung microbiota. Alterations in microbial composition have been observed in lung cancer patients and may contribute to disease progression. Systemic chemotherapy, while targeting cancer cells, also exerts systemic effects that may disrupt gut and lung microbiota, leading to dysbiosis. These changes may influence treatment response, immune modulation, and clinical outcomes in lung cancer patients. This narrative review explores the role of the gut-lung axis in lung cancer and examines the impact of systemic chemotherapy on gut and lung microbiota. Understanding the interaction between chemotherapy and the gut-lung axis may provide insight into potential adjuvant strategies to improve treatment effectiveness and patient quality of life.

Keywords: Chemotherapy, gut-lung axis, lung cancer, microbiota.

ABSTRAK

Insiden kanker paru terus meningkat secara global dengan angka mortalitas yang diperkirakan mencapai 18% di seluruh dunia. Penatalaksanaan kanker paru saat ini berfokus pada skrining dini, terapi dini, dan perawatan paliatif. Namun, pendekatan yang lebih mendasar masih diperlukan untuk meningkatkan luaran pengobatan. Aksis usus–paru menjadi salah satu fokus penting karena berperan dalam pertahanan sistem paru dan dipengaruhi oleh perubahan mikrobiota usus dan paru. Perubahan komposisi mikrobiota telah ditemukan pada pasien kanker paru dan diduga berkontribusi terhadap progresivitas penyakit. Kemoterapi sistemik, selain menargetkan sel kanker, juga memberikan efek sistemik yang dapat mengganggu keseimbangan mikrobiota usus dan paru, sehingga menyebabkan disbiosis. Kondisi ini berpotensi memengaruhi respons terapi, modulasi imun, dan luaran klinis pasien kanker paru. Ulasan ini membahas peran aksis usus–paru dalam kanker paru serta dampak kemoterapi sistemik terhadap mikrobiota usus dan paru. Pemahaman mengenai interaksi ini diharapkan dapat membuka peluang strategi adjuvan untuk meningkatkan keberhasilan terapi dan kualitas hidup pasien. **Indry Agatha Rihi Pake, Widiya Hari Kurnia, Mirna Nastiti Louqi Machfud, Stella Pangestika, Candra Muhammad Yusuf Hidayatullah, Arya Marganda Simanjuntak. Implikasi Klinis *Gut-Lung Axis* pada Kemoterapi Sistemik untuk Kanker Paru.**

Kata Kunci: Kemoterapi, aksis usus-paru, kanker paru, mikrobiota.

https://doi.org/10.55175/cdk.v53i02.1699

INTRODUCTION

As a leading case of cancer in the world, the Global Cancer Observatory (GLOBOCAN) indicates a rapid increase in new cases of diagnosis in lung cancer, as shown by data from 2018 that estimates 2.094.0000 to 2,206,771 in 2020 global data, with an estimated 1,796,144 (18%) of new death cases all around the world.[1,2] Lung cancer is the second cancer in men after prostate cancer and the second cancer in women after breast cancer. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, there were an anticipated 229,000 new cases and

Alamat Korespondensi *arya.marganda@gmail.com*

deaths from lung cancer in the United States in 2020, accounting for 12.7% of all cancer diagnoses. New cases are now increasing by 2,206,771 (11%), with new fatalities accounting for 1,796,144 (18%).[1–3]

In dealing with lung cancer cases, early detection, early therapy, and palliative care are strategies in dealing with it.[4–6] However, a more fundamental approach is needed so that we can provide better therapy in the future. The gut-lung axis is one of the current focuses on the role of lung functional resilience and its interaction with lung cancer.[7] The gut-lung axis has often been discussed lately, as the role of the digestive and respiratory systems is interrelated.[7] It appears from research that if a patient has an imbalance of gut microbiota (dysbiosis), there is a susceptibility to viral infections of the lungs.[8,9]

Not only that, but there is now a debate concerning the involvement of the gut-lung axis in the pathogenesis of lung cancer.[10] Changes in the lung and gut microbiota are linked to the advancement of lung cancer. Several studies have found that these changes promote lung cancer development and progression by influencing metabolic pathways, limiting cell function, and producing proinflammatory molecules.[11,12] Some things need to be explored further, apart from the pathogenesis itself. What is the impact of chemotherapy given to lung cancer patients on the gut-lung axis? Chemotherapy is known to have an impact not only on the cancer cells themselves but also systemically, and these changes may alter the microbiota of both the lung and gut. Therefore, the aim of this review is to explore this further. The novelty of this review is that it comprehensively explores the gut-lung axis and chemotherapy, which has been minimally explored to date.

Lung Microbiome in Healthy and Lung Cancer Patients

Normal lungs are typically assumed to be sterile. However, current investigations have revealed that they also house microbial populations, including *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria*.[13–16] Comparison to the upper respiratory tract, the microbiota of the lung mucosa is more phylogenetically diverse. Furthermore, the lower respiratory system is primarily constituted of Pseudomonas, *Streptococcus*, *Fusobacterium*, *Megacoccus*, and *Sphingomonas*.[16,17] In normal conditions, the microbiome has some functions, such as maintaining the equilibrium of homeostasis and improving immune capability. The respiratory system is the primary point of constant interaction with foreign germs. The airway epithelium acts as a sensor for the presence of microorganisms, and its epithelial cells are in constant contact with the environment. This link is essential for maintaining stable homeostasis. The environmental conditions necessary for microbial growth in the respiratory tract (such as pH, temperature, nutrition, oxygen tension, and host inflammatory cell activity) vary, resulting in substantial geographic variation within a single healthy lung.[18] In health settings, the microbiome can have an impact on immune function. Symbiotic fungi have been shown to influence the immune system and control bacterial populations, hence assisting in the restoration of bacterial ecology after antibiotic therapy.[19,20]

The lung microbiota of lung cancer patients, for example, the non-small cell lung cancer (NSCLC) group, was enriched at the phylum level for *Firmicutes* and *Bacteroidetes*, with *Streptococcus*, *Prevotella*, and *Veillonella* ranking first through third. These investigations imply that changes in the dynamics of bacteria are intimately linked to the development of illnesses such as lung cancer. Differences in the lung microbiota are indicated in **Figure 1**. The lung microbiota governs the host's pulmonary immune system, and a balance between pulmonary immunity and bacteria is essential for infection resistance. Dysbiosis of the lung microbiota can activate resident immune cells, such as M1 macrophages and γδ T cells, resulting in oxygen-free radicals and gene alterations that promote lung carcinogenesis.[21,22]

Prevotella is a periodontal pathogen that secretes peptides through proteinase-activated receptors (PARs), which control proliferation, apoptosis, immunology, cytokine production, and microenvironmental inflammation in oral squamous cell carcinoma. Gram-positive (*Streptococcus*) and gram-negative (*Escherichia coli*) bacteria can cause distant metastatic lung cancer (NSCLC) by activating TLR 2/4 and secreting IL-6.[23–25] *Veillonella parvula* was discovered to strongly accelerate the advancement of large cell carcinoma in mice, which is consistent with its ability to boost the formation of lung adenocarcinoma in KPA mice. As a result, research reveals a role and potential mechanisms for how variations in the number of core genera influence lung cancer growth. Furthermore, the importance of a lower number of groups in lung cancer should not be overlooked; more study is required to investigate additional pathogenic species and their modes of action.[22] Tumor cells have three main biological characteristics: proliferation, invasion, and metastasis.[26] The human microbiome can directly or indirectly influence lung cancer cell proliferation, invasion, metastasis, genomic instability, and mutations (**Figure 2**).[27]

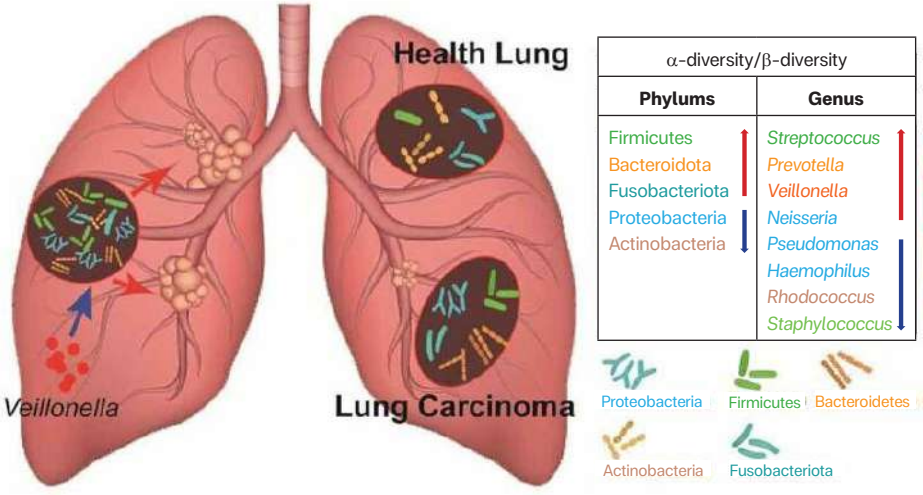

Figure 1. Comparison of lung microbiome in healthy and lung cancer patients.[22]

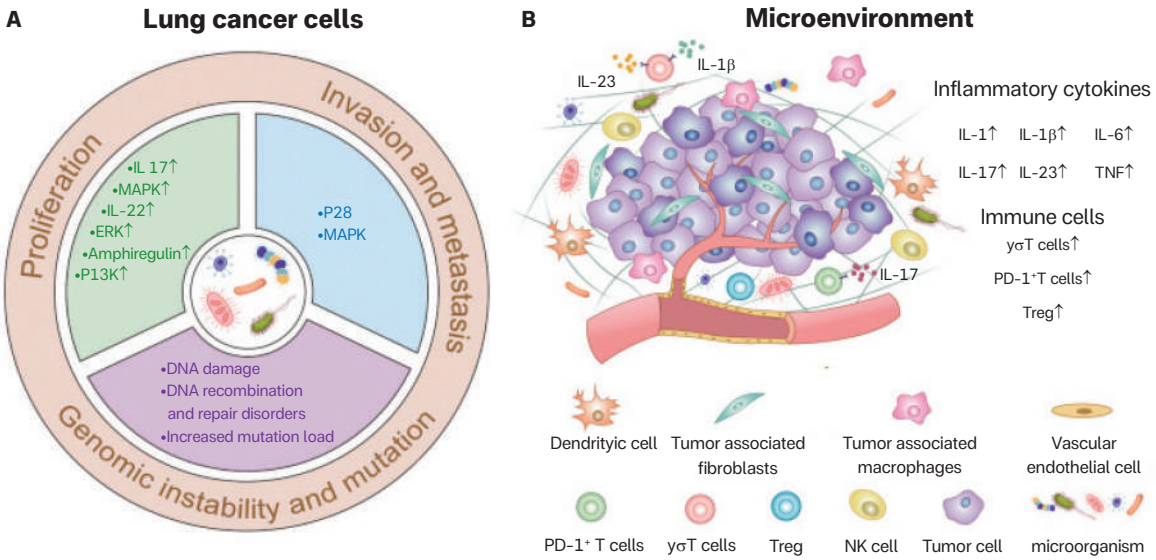

Figure 2. Impact of human microbiome on lung cancer pathogenesis **(A)** Human microbiome can influence lung cancer cell proliferation, invasion, metastasis, genomic instability, and mutation. **(B)** Human microorganisms help to shape the lung cancer microenvironment (TME) and impact the beginning and course of the disease by boosting the expression of immune cells and inflammatory factors.[27]

Abbreviations: IL: Interleukin; MAPK: Mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase; P13K: Phosphoinositide 3-kinase; P28: 28 amino acid peptide; PD-1+(superscript): Programmed cell death protein 1; Treg: Regulatory T cells; NK: Natural killer

Lung cancer frequently has lower airway microbiota and oral symbiotic bacteria, which can activate the host transcriptome implicated in carcinogenesis. The lower airway transcriptome's extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) signaling pathways are markedly elevated in lung cancer patients relative to healthy individuals, which is associated with the enrichment of diverse microbiome groups in the lower airways.[28] A recent research also discovered that the most prevalent bacterium, *Vibrio*, is responsible for the upregulation of the PI3K, ERK, mitogen-activated protein kinase (MAPK), and interleukin (IL)-17 pathways in the airway transcriptomes of patients with lung cancer. These pathways are linked to a poor prognosis.[28] Despite tremendous advancements in lung cancer oncology during the past three decades, patients with advanced lung cancer have a poor prognosis and few treatment options. Better lung cancer treatments and early detection are therefore becoming more crucial. Current research into microorganism clinical uses is in its early beginnings, with probiotics, nutrition therapies, and fecal transplantation in the preclinical model. Gaining knowledge about the connection between lung cancer and human microbiota—especially gut microbiota—may lead to novel discoveries about lung cancer detection and treatment.[29]

Gut-Lung Axis at a Glance

Although the gut and lungs are structurally separate, putative anatomical linkages and complicated pathways involving their respective bacteria have confirmed the presence of a gut-lung axis (GLA).[30] The intricate interactions between the gut microbiota and the human immune system have important local impacts on the gut, as well as adjacent tissues and organs such as the lung (**Figure 2**).[27] The gut microbiota can alter not just the lungs' homeostasis, increasing susceptibility to lung illness, but also the lung's resistance and recovery ability. Changes in gut microbe composition and metabolic processes induced by the environment, nutrition, illness, or related medical treatments (such as antibiotics) have an impact on the immune response and respiratory tract homeostasis.[31] Insoluble One of the most significant and interconnected ways that gut microbiota contributes to pulmonary diseases is through microbial components that circulate along the gut-lung axis. Antigens produced from the microbiota influence pulmonary immunological homeostasis by participating in the gut-lung axis of the host immune response.[31]

The gut-lung axis **(Figure 3)** is a bidirectional relationship represented by a circle that may be triggered from both sides. The digestive and respiratory tracts' epithelial surfaces are exposed to a variety of microorganisms. The bacteria consumed can enter the gastrointestinal system and subsequently, via aspiration, the respiratory tract. The mucous membranes of the intestines and lungs act as a barrier against microbial invasion. Colonization by normal microorganisms and pathogenic germs will cause an inflammatory reaction. The transmission of commensal bacteria in the colon, such as SFB, Bifidobacterium, and Bacteroides, also causes the synthesis of antimicrobial peptides, immunoglobulin A, and inflammatory cytokines.[7,10]

Various biotic interact closely inside each organ, either directly or indirectly modifying one another. The gut microbiota regulates both the gut and lung immune systems through local or long-range interactions that include CD8+ T cells, Th17, IL-25, IL-13, prostaglandin E2, and/or NF-kB-dependent pathways. The lung microbiota influences mucosal immunology and contributes to immunological tolerance by recruiting neutrophils, producing pro-inflammatory cytokines via receptor 2 (TLR2), and releasing antimicrobial peptides such as β-defensin 2, activated by T helper 17 (Th17) **(Figure 4)**.[7,30]

In addition to influencing inflammatory cytokines, the microbiome generates metabolite products. The gut microbiota

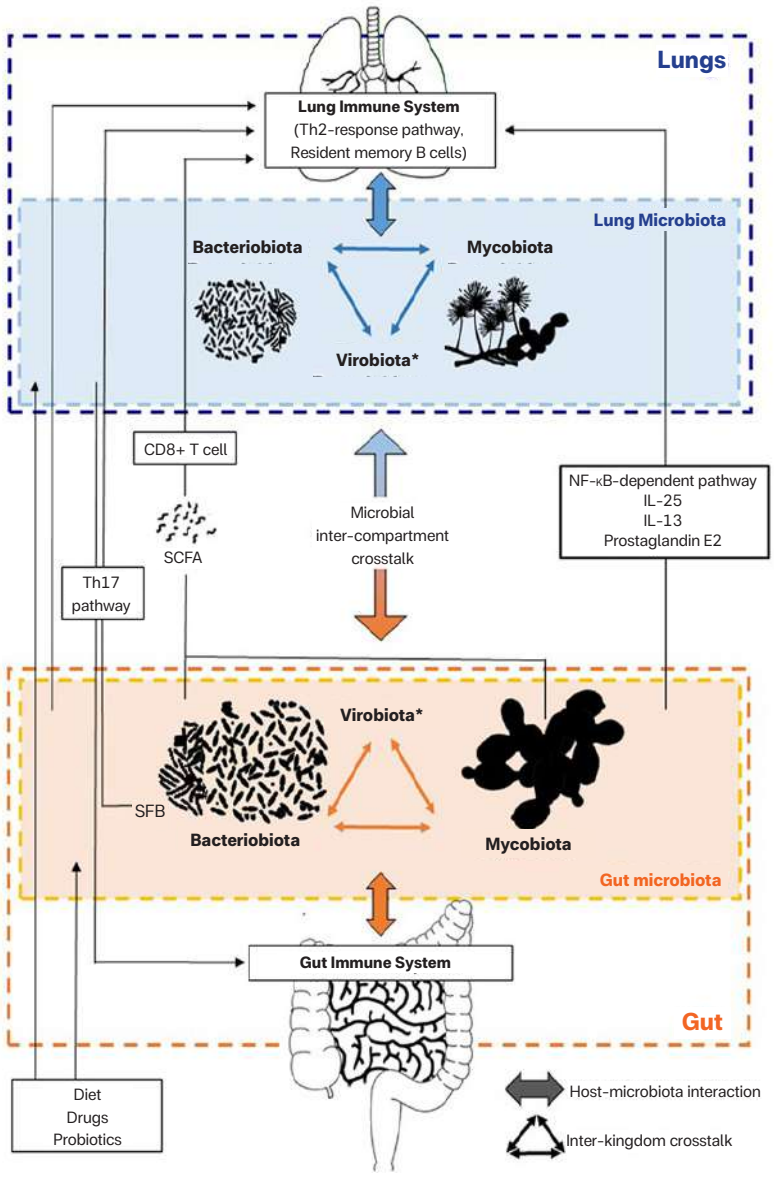

Figure 3. Inter-kingdom and inter-compartment interactions in the gut-lung axis.[7]

ferments undigested food fibers to produce short-chain fatty acids (SCFAs), the most prevalent of which are propionate, acetate, and butyrate. SCFAs go from the stomach into the circulation, where they might reach the bone marrow and induce hematopoiesis. In the bone marrow, hematopoietic stem cells (HSCs) can develop into multipotent progenitors (MPPs), which can then commit to common lymphoid or common myeloid precursors. CMPs can develop into granulocyte and macrophage progenitors (GMPs), which eventually become monocyte and DC progenitors. MDPs can produce both Ly6C– and Ly6C+ monocytes, as well as common DC precursors (CDPs). Monocytes can exit the bone marrow and circulate as patrolling Ly6C– or inflammatory Ly6C+ monocytes in the peripheral tissues. Ly6C+ monocytes in the lungs can differentiate into CD11b+ monocyte-derived DCs (moDCs) in response to inflammation. CDPs differentiate into pre-classical DCs (pre-DCs), which move from bone marrow to the lungs and mature into CD103+ or CD11b+ conventional DCs (cDCs). Ly6C-negative monocytes can develop into alternatively activated macrophages (AAMs). Propionate and acetate were shown to increase MDP and CDP production during allergic airway inflammation caused by house dust mites (HDMs). These inflammatory DC precursor cells move to the lung and develop into CD11b high DCs with high phagocytic capability but low activation, as seen by lower expression of CD40, PD-L2, and CD86. As a result, these lung DCs have a decreased ability to stimulate T helper 2 (Th2) effector function and proliferation, and so cannot support Th2 cell-mediated allergic airway inflammation.[7,31,32]

Gut-Lung Axis Role in Lung Cancer

Lung cancer is one of the malignant tumors with the highest morbidity and mortality in the world.[33] Currently, Bacteria identified can contribute significantly to the development of lung cancer. Various microbiomes live in the human body and help to maintain a dynamic and stable microenvironment. Although microbial populations are necessary for human health, disrupting homeostasis can have a negative impact on human health. Dysregulation of the microbiome has been linked to several illnesses. According to studies, an imbalance in microbial populations in certain organs is linked to carcinogenesis, either directly or indirectly.[29]

When compared to healthy controls, lung cancer patients' gut microbiomes show significant changes in both composition and function, as demonstrated by a decline in intestinal microbial diversity and metabolically linked biological activity. Microbiome dysbiosis causes genotoxic and pathogenic consequences, alters the host's inflammatory response, and throws off the cell cycle. It also creates metabolic chemicals that cause cancer.[10,29]

Large immune cell populations, such as mesenteric lymph glands in the intestinal tract or submucosal layer macrophages, start the inflammatory process, and the gut microbiota supplies molecular patterns associated with pathogens (PAMPs) of different microbial origin. On the surface of intestinal epithelial cells (IECs) exist pathogen recognition receptors called toll-like receptors (TLRs). They recognize a wide range of microbial ligands, including fungi, parasites, and lipopolysaccharides (LPSs), as well as multibranched RNA viruses. The protein component of living or dead bacteria, along with pieces of their cell walls, can enter the chyli cisterna through the mesenteric

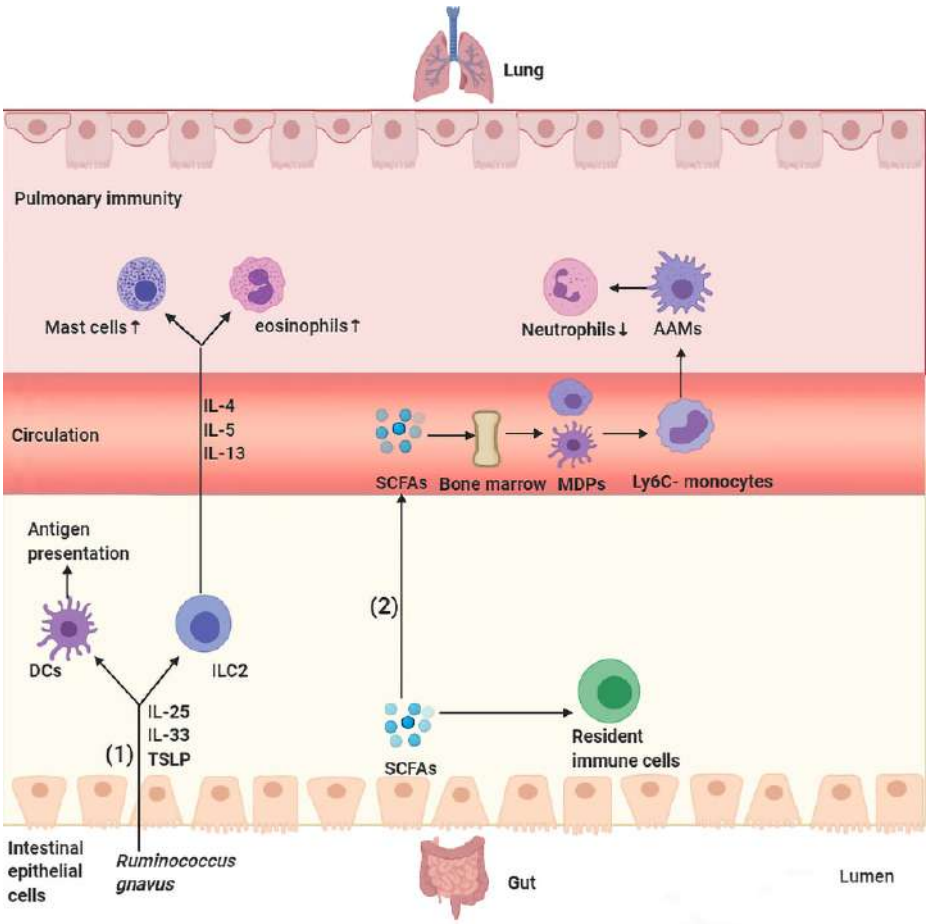

Figure 4. Major communication channels within the gut-lung axis.[31]

Abbreviations: AAMs: Alternatively activated macrophages; IL: Interleukin; TSLP: Thymic stromal lymphopoietin; SCFAs: Short-chain fatty acids; MDPs: Monocyte-dendritic cell progenitors; Ly6C: Lymphocyte antigen 6 complex.

lymphatic system and bypass the cytokines and chemokines produced in the intestine to enter the gut circulation if the microbial ligand is not removed by the initial line of defense. Once these ligands enter the lungs, they trigger the inherent adaptive immunity of TLRs, which in turn triggers T cell activation and differentiation along with the activation of macrophages and dendritic cells. Furthermore, commensal bacteria that migratory bacteria feed on emit compounds, including propionate, butyrate, and SCFAs that directly stimulate intestinal epithelial cells and regulate the release of immune cells. After digestive enzymes break down dietary fiber, gut bacteria absorb a type of metabolite called short-chain fatty acids (SCFAs).[10,34]

Human metabolism may be impacted by a variety of microbial bioactive substances that are present in the microbiome. For instance, the secondary bile acids produced by gut bacteria, deoxycholic acid and lithocholic acid, harm DNA and are connected to the onset of cancer. Genotoxic imbalances and compositional changes in bacteria can produce a variety of toxins, increase the production of free radicals, cause DNA lesions, cell cycle arrest, and death in the absence of DNA repair. Therefore, changes in the microbiome have the potential to cause cancer in the host organism. Moreover, colon mucous membranes, which are the first point of contact with the antigen, are stimulated by immune cell migration.[10]

The Effect of Systemic Chemotherapy in Lung Cancer on Gut and Lung Microbiome

Chemotherapy for cancer might be considered as yet another major irritant for the gut microbiota. Chemotherapy treatments can alter the makeup of the gut microbiota. In addition to affecting gut homeostasis, impairing mucosal barrier integrity, and allowing bacteria to translocate into the lamina propria and perhaps throughout the body, it induces a significant inflammatory response.[35]

Chemotherapy's effects on the gut microbiota might be direct or indirect, which means they can manifest as major side effects such as hepatoxicity, neurological symptoms, myelosuppression, gastrointestinal toxicity, and malnutrition. Following chemotherapy treatments, over 80% of oncological patients have diarrhea, infections, nausea, and stomach pain, which are the most common side effects. Underlying reasons include gastrointestinal tract mucosal barrier loss, which can lead to mucositis, malabsorption, and epithelial cell death, all of which contribute to (and are exacerbated by) gut microbiota change.[36] Chemotherapy is a powerful stressor on the gut microbiota, causing it to become unstable and temporary, after which it may or may not rebound to its original condition.[37]

Hysteresis, a new, enduring condition of health or malaise brought on by chemotherapy, can lead to disruptions that encourage the growth of new diseases. Chemotherapy-responsiveness of the gut microbiota is regulated by an intricate and diverse mechanism. These factors include those related to the chemotherapy regimen (e.g., the kind and dosage of anticancer drugs), as well as the patient's demographics, anthropometric measurements, biochemical and other laboratory results, stage of the disease, co-administration of other medications, dietary and immunological factors, and, of course, the initial composition of the gut microbiota. Chemotherapy patients in particular have significantly reduced oral intake due to the severe side effects of the medicine, which include the enteral mucositis and nausea mentioned earlier.[37] This decline in the patient's nutritional state may aggravate gut microbiota dysbiosis and mucosal damage caused by mucositis, resulting in poor clinical outcomes.[38]

Chemotherapy can cause dysbiosis in the gut microbiome through several mechanisms:[39]

1. **Direct toxicity to microbiota**
   Chemotherapeutic medicines, which are particularly meant to target cancer cells, can also destroy fast-dividing cells in the gut lining. This may result in a decline in the type and amount of beneficial gut

bacteria because these germs may be more vulnerable to the harmful effects of chemotherapy.

2. **Alteration of the gut environment**
   Chemotherapy can disturb the gut ecology by inducing inflammation, pH abnormalities, and alterations to nutritional availability. These alterations can promote the growth of pathogenic bacteria while suppressing good ones, resulting in a microbiota imbalance.
3. **Antibiotic use**
   Antibiotics are commonly administered to cancer patients in order to treat or prevent infections during chemotherapy. Antibiotics can promote dysbiosis by removing a wide range of bacteria, including beneficial ones, further disrupting the gut microbiome.
4. **Immune System Suppression**
   Chemotherapy typically lowers the immune system, making it difficult for the body to fight hazardous bacteria. This may promote the growth of harmful microorganisms, worsening dysbiosis.
5. **Gastrointestinal Toxicity**
   Chemotherapy side effects include nausea, vomiting, diarrhea, and mucositis, which can alter food intake and gut motility, thereby affecting the microbiome composition and causing dysbiosis.

Prebiotics, probiotics, and fecal microbiota transplantation (FMT) have the ability to manipulate the gut microbiome and enhance recovery following chemotherapy.[39] Prebiotics are described as "a substrate that is selectively utilized by host microorganisms conferring a health benefit".[40] Prebiotics undoubtedly help to maintain gut microbiota resistance and resilience, despite the fact that little is known about their use in cancer patients. The formation of syntrophic cross-feeding relationships, which are critical for the ecological health of GM, is explicitly recognized to be a component of their metabolism. As a result, this metabolism may encourage the survival and/or repopulation of beneficial commensals, thereby accelerating the restoration of microbial diversity and abundance.[41,42]

"Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" is how probiotics are defined. By repairing the composition and health-related functions of the gut microbiome, probiotic use can aid in the prevention of infections and the growth of undesirable bacteria. The fundamental mechanisms encompass rivalry for receptor and binding sites, preservation of intestinal mucosal integrity, and the production of an assortment of chemicals, such as antibacterial substances, among others.[40,43]

The process of transferring healthy donor feces into a patient's digestive tract in order to improve overall diversity and restore gut microbiome functioning is known as fecal transplantation. Prebiotics, probiotics, and other gut microbiome modification techniques have shown promising results, but little attention has been paid to whether, to what extent, and how quickly they facilitate the restoration of a eubiotic gut microbiota.[39,44]

Chemotherapy has the power to profoundly modify the intestinal environment, causing changes in the makeup of the gut microbiota, inflammation, and the disintegration of the mucosal barrier. This disruption may lead to a sustained state of recovery or non-recovery, depending on the initial microbiota condition and other treatment-related characteristics **(Figure 5).** A more varied microbiota and the existence of founders or keystone taxa that can encourage the repopulation of other commensals in order to swiftly

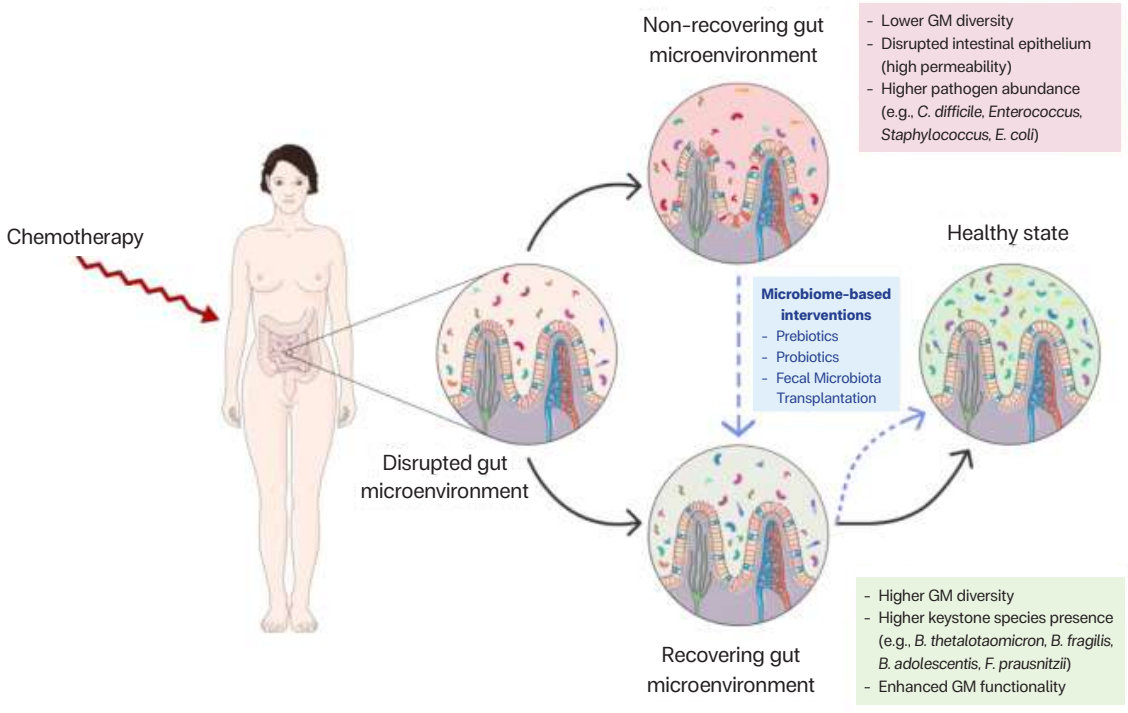

Figure 5. The gut microbiome recovers following chemotherapy treatment.[39]

reestablish a healthy eubiotic environment are characteristics of the recovery state that set it apart. Reduced diversity of the gut microbiota and higher proportions of pathobionts—whose colonization and growth may be facilitated by the elimination of rival beneficial commensals in an inflammatory milieu—as well as a disturbed intestinal epithelium are characteristics of the non-recovery state. Prebiotics, probiotics, and fecal microbiota transplantation are examples of microbiome-targeted interventional therapies that may help patients move from non-recovery to recovery by hastening the restoration of a healthy gut microbiota structure and guarding against the long-term effects of chemotherapy.[39]

Immunotherapy, particularly immune-complex inhibitors (ICIs), has demonstrated extraordinary performance while posing a low risk of toxicity and side effects, making it a prospective therapeutic option for advanced non-small cell lung cancer. Studies have found a substantial relationship between the gut microbiota and the immunotherapy response of tumor patients, implying that it might be used to predict the efficacy of tumor immunotherapy. Ren, *et al*., showed that fecal microbiota transplantation (FMT) has become an intriguing technique to boost immunotherapy in cancer patients by restoring a healthy gut flora. The Responders (R) group showed increased gut microbial diversity of alpha and beta, as well as Bacteroidetes and Actinobacteriota, compared to the Non-responders (NR) group ($p < 0.05$). In addition, the R group showed significantly greater numbers of *Faecalibacterium* ($p = 0.000969$), *Ruminococcus* ($p = 0.04891$), *Lachnospiraceae* ($p = 0.03034$), *Eubacterium* ($p = 0.04603$), and *Clostridia* ($p = 0.0008736$) than the NR group. The study on *Faecalibacterium* found that the gut microbiota is significantly diversified (95% CI: 0.66–0.94) and performs important roles in immunotherapy for patients with NSCLC. There were no phylum-level alterations in species composition of the microbiota before and after ICI treatment. Nonetheless, immunotherapy resulted in a substantial rise in the species *Faecalibacterium* ($p = 0.02813$). During the study of the relationship between gut microbiota and SCFA (short-chain fatty acid analysis), *Faecalibacterium* in the R group showed a favorable connection with butyrate.[45]

Anticancer therapies such as cisplatin-based therapy and albumin-bound paclitaxel are widely utilized in the treatment of lung cancer. The complicated ecology of billions of microorganisms that make up the human gut microbiota has sparked a lot of interest in study due to its major influence on host physiology, nutrition, and immunity. An increasing amount of evidence suggests that anticancer treatment may significantly alter the makeup of the gut microbiota, thereby negatively impacting health. Post-cancer therapy may injure intestinal epithelial cells, resulting in dysbiosis of the gut microbiota. The result is a significant fall in the number of anaerobic bacteria (such as Bacteroides, *Clostridium*, *Prevotella*, and *Bifidobacterium*) and *Streptococcus*, resulting in ectopic gut microbiota and major structural changes.[46] We investigated the changes made to the gut microbiota of patients with non-small cell lung cancer (NSCLC) after anticancer treatment, based on previously mentioned research. *Firmicutes* and *Bifidobacterium*, both members of the Actinobacteriota class, are often found in healthy guts and have been linked to a variety of health advantages. Firmicutes help in the digestion of complex carbohydrates and produce short-chain fatty acids that are beneficial to the stomach. Bifidobacterium is well-known for its capacity to manufacture vitamins, enhance barrier function, and decrease intestinal inflammation. Following anticancer therapy, decreasing *Firmicutes* and *Bifidobacterium* abundance may influence these beneficial activities, potentially affecting gut health and overall patient well-being.[47]

Chemotherapy regulates the immune system; hence, the concept of immunomodulatory ability applies. Cyclophosphamide's well-known anticancer and immunomodulatory effects led to its registration as a therapy for both early-stage and metastatic breast cancer. This alkylating agent alters the microbiota in the small intestine in a transgenic tumor mouse model of autochthonous lung carcinogenesis, causing the translocation of specific Gram-positive bacteria into secondary lymphoid organs, including *Lactobacillus johnsonii* (which grows in more than 40% of cases), *Lactobacillus murinus*, and *Enterococcus hirae*. Gram-positive bacteria activate the memory Th1 immune response as well as the development of a specific fraction of "pathogenic" T helper 17 (pTh17) cells. When these microorganisms are absent from germ-free or antibiotic-treated animal models, the pTh17 response and cyclophosphamide tumor resistance decrease. Cyclophosphamide's anticancer efficacy was largely restored by the adoptive transfer of pTh17 cells. These data suggest that in LC patients, the gut microbiota modulates the anticancer immune response.[48]

This review only discusses the effects of systemic chemotherapy in lung cancer that can change the microbiota of the gut and lung. However, it does not rule out the possibility that other cancers can have the same effect or impact with the use of other systemic chemotherapy, thus opening up opportunities for further study of the impact of chemotherapy on dysbiosis and other manifestations in other cancer systems (other than lung cancer).

Implications Towards Lung Cancer

The Gut-Lung Axis plays a role in the defence of the pulmonary system and can be affected by lung cancer, and chemotherapy and other therapies can change its composition (dysbiosis). As already shown, changes in the composition of the gut and lung microbiota in lung cancer can increase the aggressiveness and even favour metastasis of the cancer.[23–25] This suggests that dynamics in gut microbiota can worsen the patient's condition, and the Gut-lung axis approach may influence the progression of lung cancer, the success of lung cancer therapy, and the patients' quality of life. However, scientific research on the elaboration of the gut-lung axis in cancer patients is still limited, especially when receiving chemotherapy and antibiotics that are considered for infection prophylaxis.[49]

Gut-lung axis approach opens up the potential for adjuvant therapies to support treatment or to minimise side effects of chemotherapy. Some potential adjuvants are fecal transplant, biotic supplements such as prebiotics, probiotics, or synbiotics. Biotic supplementation seems more promising due to better accessibility and possibly more affordable. There is currently an interesting discussion regarding fecal transplantation and biotic supplementation in cancer case management (not limited to lung cancer).[50] The role of the Gut-lung axis in treatment and

prevention is still much to be explored as an approach to dysbiosis.

With the possibility of this new approach, a more comprehensive management of lung cancer can be developed, by not only focusing on the cancer cells, but also in terms of microbiota that supports the patient's immunity, which may be the most important part of the treatment.

Screening for gut and lung microbiota is currently not widely accessible and may be costly, but if it can support the quality of care for cancer patients, wider clinical use may reduce costs.

The provision of biotic supplementation is considered affordable and has good accessibility, but has not yet been the focus of research; another potential benefit is whether it can reduce medical costs due to opportunistic diseases, because the immunity is supported by the microbiota. There have been no studies directly looking at changes in the lung microbiome and gut microbiome during the process of chemotherapy. This implication is based on the connection between previous findings of the impact of chemotherapy on the microbiota in the body and how it is a manifestation of dysbiosis that is also found in lung cancer patients. Given that this has not been studied directly, it is hoped that this article will support the theory to facilitate or induce other researchers to start research on this matter.

Is the Gut Microbiota System Limited in Systemic Chemotherapy?

As previously explained, systemic chemotherapy not only attacks lung cancer cells, but also affects other healthy cells, especially in this aspect of the discussion, the gut microbiome and lung microbiome, which continues to affect the condition of the patient. There are several other therapeutic modalities, such as radiotherapy and resection surgery, but the impact on the gut and lung microbiome is not yet known because there are no studies that examine this. This opens up opportunities for research on the impact of other therapeutic modalities in lung cancer on changes in the microbiota of two realms (gut and lung). Potential alterations in the gut flora in patients receiving chemotherapy are described in the review paper by Liu, *et al*., 2021. According to the study, radiotherapy might alter the microbiota's makeup, favoring dysbiosis, which can have an impact on the patient's health while receiving treatment.[51] In their 2015 study, Kim, *et al*., examined the gut microbiota of mice who received radiation treatment for gastrointestinal tract cancer. They found that radiation therapy can alter the gut microbiota, particularly by increasing the number of bacteria belonging to the Cornebacterium genus.[52] Therefore, gut microbiota may not only be affected by systemic chemotherapy, but also could be due to other therapies such as radiotherapy, and may also be affected by other types of therapy such as immunotherapy; however, the study to confirm data is still minimal.

CONCLUSION

Chemotherapy has the potential to disrupt the composition of gut microbes, potentially disrupting the Gut-lung axis, which plays a role in the defense of the pulmonary system. The role of adjuvant probiotics, prebiotics, or synbiotics in the management of cancer requires further study.

Acknowledgments

We would like to thank MedHub Academy for the support and advice.

Declaration of Interest

There is no conflict of interest among all authors.

Funding

This manuscript has not received any funding from any organization or individual.

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