CHAPTER 10

Chemotherapy and Immune System: Strategies to Modulate Immune Responses for Improved Outcomes

AYESHA SIDDIQA[1], NEHA ANEES[1], SYEDA SANIA ZAHARA[1], NAKASH MASIH[2*], AKASH NADEEM[1], MARRIUM BIBI[1], MUHAMMAD TARIQ[1], ANEES UR RAHMAN[1]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[2] Institute of Molecular Biology and Biotechnology, The University of Lahore, Lahore, Pakistan
[*]Corresponding author: 70142564@student.uol.edu.pk

SUMMARY

Anti-cancerous medications surround a diverse range of drugs designed to counter the growth and metastasis of cancer cells. Ranging from traditional chemotherapy agents to targeted therapies and immunomodulators, these medications aim to disrupt various aspects of cancer cell biology and enhance the body's natural defenses against different malignancies. Chemotherapy plays a fundamental role in cancer treatment and employs powerful drugs to halt or kill rapidly dividing cells, including cancer cells. While effective in eradicating tumors, chemotherapy can also impact healthy cells, leading to different impairments in the body. This approach is integral in curative and palliative care, often used in combination with other therapies to achieve integrated cancer management. Chemotherapy induces various alterations in the immune system, influencing short-term and long-term responses. While certain agents stimulate immunogenic cell death, releasing signals for immune recognition, others may cause immunosuppression, impairing the body's ability to defend against infections. Different strategies to modulate immune responses have emerged as pivotal components of modern therapeutic approaches. From immunotherapy advancements to personalized interventions targeting the microbiome, these strategies aim to accelerate the body's natural defenses against cancer. Understanding the intricacies of immune modulation is imperative for exploring treatment plans, maximizing therapeutic benefits, and minimizing adverse effects. Therefore, this chapter explores the connection between chemotherapy and the immune system and strategies to modulate immune responses for improved outcomes.

INTRODUCTION

Cancer has emerged as a significant and growing concern globally which induces profound challenges to public health, the healthcare system and societies worldwide. The number of cancer cases has steadily escalated over the past few decades, ultimately affecting numerous populations and age groups worldwide (Hood & Flores, 2012). Numerous factors i.e., alterations in lifestyle, aging populations, pollution in the environment as well as genetic predispositions are reported for this substantial increase. Risk factors for cancer including poor food, sedentary behavior as well as exposure to carcinogens, are more common when populations experience demographic shifts and embrace more urbanized as well as industrialized lifestyles (Irigaray et al., 2007).

The global influence of cancer is elevated beyond the domain of health, deteriorating economies along straining healthcare infrastructures. The financial load connected with cancer treatment, diagnosis as well as long-term care has a substantial outcome on affected individuals and healthcare systems (Berns et al., 2020). Chemotherapy is reported as one of the most frequently employed cancer treatment modalities and it is effective in combating different types of ailments. Strong pharmaceuticals are employed in this type of anti-cancer remedy to precisely target as well as eradicate cancer cells that divide rapidly, averting them from spreading and increasing. Chemotherapy has been recognized for its capability to diminish tumors as well as halt the spread of cancer, but since it is non-selective, it frequently has side effects that damage some healthy cells in development (Feng & Chien, 2003).

Regardless of these challenges, chemotherapy continues to be a fundamental part of numerous cancer treatment approaches, whether used alone or alongside other therapies. Moreover, the interaction between chemotherapy and the immune system is complicated and plays an indispensable role in determining the effectiveness of the treatment (Spadi et al., 2016). Chemotherapy disturbs the body's immune system, which is indispensable for identifying and eradicating aberrant cells, in addition to directly influencing cancer cells. Unfortunately, certain chemotherapy medicines have the side effect of constraining the bone marrow's capability to produce

How to Cite: Siddiqa A, N Anees, SS Zahara, N Masih, A Nadeem, M Bibi, M Tariq & AU Rahman, 2024. Chemotherapy and immune system: Strategies to modulate immune responses for improved outcomes. In: Zoology: Advancements and Research Trends (Ijaz MU, N Ehsan, M Imran & S Yousaf, eds): FahumSci, Lahore, Pakistan, pp: 70-78. ISBN: 978-627-7745-02-8. https://doi.org/10.61748/Zool.2024/10

white blood cells, which are vital to the immune system. Immunosuppression resulting from this destruction may upsurge a patient's vulnerability to infections (Gun et al., 2019). Regulation of the delicate equilibrium between eliminating cancer cells and conserving immune function is a continuous problem in cancer treatment. Therefore, in this chapter, we will discover the connection between chemotherapy as well as the immune system and approaches to control immune responses for enhanced outcomes.

CHEMOTHERAPY AND IMMUNE SYSTEM INTERACTION

One of the primary mechanisms through which chemotherapy affects the immune system is bone marrow suppression. Chemotherapy drugs, designed to target rapidly dividing cells, inadvertently impact the bone marrow's ability to produce blood cells, including those crucial for immune function (Ahlmann & Hempel, 2016). White blood cells, particularly neutrophils, lymphocytes, and monocytes, are significantly affected. Neutropenia, a common side effect, results in a decreased number of neutrophils, leaving patients more susceptible to infections. The immunosuppressive effect of chemotherapy poses a delicate balance between eliminating cancer cells and compromising the body's natural defenses (Zhang et al., 2022).

T cells are central players in the immune response, modulating the body's defense against infections and abnormal cells, including cancer. Chemotherapy, especially drugs such as cyclophosphamide and paclitaxel, can impact T-cell function (Truong et al., 2021). While the exact mechanisms are intricate and drug-specific, some chemotherapy agents induce apoptosis, or programmed cell death, in dividing T cells. This temporary depletion of T cells can impair the adaptive immune response, leading to increased vulnerability to infections during and shortly after chemotherapy cycles (Mollaei et al., 2021). The creation of antibodies, which is indispensable to the immune system's capability to recognize and destroy infections, depends on B cells. Some chemotherapy medicines i.e., rituximab, target B cells particularly in order to destroy malignant B cells in conditions including lymphoma (Akkaya et al., 2020). However, this intensive approach may lead to a reduction in B cell counts, which would influence the humoral immune response. Depending on the specific chemotherapy treatment, the influence on B cells might vary; certain actions may result in temporary suppression, while others may have long-lasting results (Vazquez et al., 2015).

Both positive as well as negative modulations of natural killer cells (NK cells) function can be accomplished by chemotherapy. A reduction in the quantity as well as activity of NK cells might result from some medicines, while others positively regulate NK cell function (Zingoni et al., 2017). The intricate interplay among these actions impacts the immune response to cancer as well as recognizing how a specific medicine disturbs NK cells is indispensable for tailoring therapeutic methods (Tran et al., 2020).

Immunosuppression during treatment cycles is the direct effect of chemotherapy on the immune system. A vulnerable state is generated by lymphopenia, neutropenia as well as reduced B cell counts, which increases the danger of infections (Schirrmacher, 2019). Chemotherapy patients are commonly more susceptible to viral, fungal, as well as bacterial infections. Healthcare professionals employ supportive measures to diminish these hazards, such as prophylactic antibiotic prescriptions or the administration of growth hormones to upsurge the creation of white blood cells (Teoh & Pavelka, 2016).

It has been revealed that individuals who get chemotherapeutic treatment and have short-term immune suppression are extensively susceptible to opportunistic infections. Common infections, which are frequently modulated by a functioning immune system, can extremely damage immunocompromised people (Rapoport et al., 2021). Cytomegalovirus, Candida and Aspergillus, are a few opportunistic infections that might be hazardous after receiving chemotherapy. Keeping an eye on things, employing preventative antibiotics as well as acting quickly are all necessary to accomplish the short-term immunosuppressive effects of chemotherapeutic remedies (José et al., 2020). Chemotherapy may result in chronic immunodeficiency in specific individuals after the initial treatment stage. Patients experience varying degrees as well as durations of immunosuppression, which can be accredited to numerous variables incorporating cancer, the particular chemotherapy regimen along individual variations in immune response. Even when the chemotherapeutic regimen is over, variations in NK cell activity, poor B cell recovery, as well as long-lasting impacts on T cell function can increase the hazard of infections (Mancuso et al., 2022).

Chemotherapy can interfere with the immune system's memory function, making it more difficult for the body to mount a defense against antigens or viruses that it has already come into contact with. This effect on immunological memory is particularly important when it comes to vaccinations, since some people may become less vulnerable (Ebersole et al., 2016). Research on vaccination schedule optimization as well as vaccine effectiveness optimization is ongoing in order to address the long-term effects of chemotherapy on immunological memory (Vermaelen, 2019). However, although being used to halt the proliferation of aberrant cells, chemotherapy has the potential to activate autoimmune responses (Szczęch et al., 2017). Moreover, Table 1 provides a brief description of chemotherapy and immune system interaction.

TECHNIQUES FOR ASSESSING THE IMPACT OF CHEMOTHERAPY ON THE IMMUNE SYSTEM

Evaluation of ways chemotherapeutic treatments disturb the immune system is essential for diminishing feasible side effects and maximizing cancer treatment techniques. Numerous approaches, lab checks (Hendry et al., 2017), biomarkers as well as imaging devices are employed to estimate immune features (Fig 1). One of the effective techniques for comparing immune cellular populations as well as their stage of activation is flow cytometry. Flow cytometry enables the measurement in addition to the characterization of

B cells, T cells, and NK cells along with other immune modulators by labeling cells with fluorescent indicators (McKinnon, 2018). Using this method, medical experts and scientists can also display adjustments within the makeup of immune cells in addition to examining how chemotherapy disturbs various cellular types with the passage of time. When comparing the immune cellular dynamics during chemotherapy as well as comprehending how these alterations have an effect on treatment effects, flow cytometry could be very fundamental (Galli et al., 2020).

Variations in cytokine stages introduced by means of chemotherapy are important for governing immunological responses. The estimation of different concentrations of cytokine in blood or tissue samples is called cytokine profiling. This approach highlights the inflammatory microenvironment as well as immune system stimulation (Sharma et al., 2023). Chemotherapy possesses the ability to regulate the balance among inflammatory indicators by means of influencing the cytokines profile.

An extremely employed laboratory method for measuring certain proteins is the enzyme-related immunosorbent assay (ELISA). The portions of immunoglobulins (Ig) incorporating IgA, IgG along IgM, which might be imperative for humoral immunity, are analyzed by researchers using the ELISA technique (Mao et al., 2016). Changes in Ig awareness can offer essential facts about how chemotherapy disturbs B mobile hobby (Kartikasari et al., 2021). Besides, a blood smear gives considerable insights approximately the shape, distribution in addition to the length of immune cells. Even though it isn't as complex as flow cytometry, this traditional method is especially useful in estimating changes in the level of white blood cells in addition to spotting any anomalies (Kratz et al., 2019).

Chemotherapy regularly prompts blood cellular counts to fluctuate, resulting in decreased levels of red blood cells (anemia), platelets (thrombocytopenia) along white blood cells (leukopenia). By measuring the CBC ranges, clinical experts also efficiently examine as well as treat hematological toxicities induced by chemotherapeutic drugs, subsequently reducing the threat of infections and bleeding troubles (Kuter, 2015; Doig & Zhang, 2017). The absolute counts of lymphocytes in addition to neutrophils acquired from a complete blood matter are employed to calculate the lymphocyte-to-neutrophil ratio or NK cells. Augmented NK cellular concentrations are associated with systemic inflammation and may be a biomarker for negative prognosis in men or women having cancer. Disparities in NK cells at some stage in and after chemotherapy may provide considerable prognostic information by using dropping mild at the dynamic affiliation between immune cells along with inflammatory responses (Zahorec, 2021).

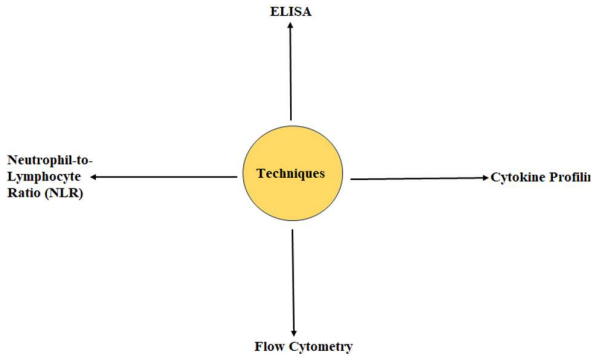

Fig 1. The most significant assessment techniques to analyze the impact of chemotherapy on the immune system

The humoral immune system's vital component particularly Ig, adversely influences as a result of chemotherapeutic medications. The useful state of B cells can be assessed with the aid of comparing Ig levels, using techniques consisting of immunofixation or immune-electrophoresis. The necessity for assisting measures encompassing Ig alternative treatment to anticipate infections in prone individuals is emphasized via the possibility that persistently minimizing Ig stages proposes a deteriorated immune reaction (Sharma et al., 2023). Chemotherapeutic drug response is regularly tracked with tumor marker assessments, together with studying alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA) in conjunction with prostate-precise antigen (PSA) (Desai & Guddati, 2023).

In oncology, positron emission tomography (PET) scans are notable diagnostic instruments that provide information on the place in addition to the metabolism of tumors. When evaluating the immune system, PET scans can display versions in tumor length and metabolic profile that could act as an oblique mediator of immunological responses (Jin et al., 2021). Assessment of how chemotherapy affects a tumor's metabolism offers statistics on how powerful a remedy is and the way it disturbs the immune system (Lewis et al., 2015). As an adaptable imaging method that amplifies the right remark of tender tissues, magnetic resonance imaging (MRI) is particularly supportive in estimating changes in the tissues, and organs, in addition to lymph nodes impacted with the aid of cancer or chemotherapeutic capsules. Apart from comparing the tumor itself, MRI can deliver information on the effect of the remedy on adjacent tissues together with feasible indications of immunological reactions. This non-invasive imaging approach advances our knowledge of the extensive time period consequences of chemotherapy on normal in addition to malignant tissues (Yuan et al., 2016).

By estimating variations in tumor density and size, computed tomography (CT) scans are often employed to evaluate how well different kinds of cancers are responding to treatment. Moreover, variations in lymph node form and distribution can be perceived on CT scans, offering information on the immune reaction. By enhancing the visibility of blood vessels and inflammatory variations on CT scans, chemicals can understand treatment-related results on immunological organs (Cutsem et al., 2016). To examine the anatomy as well as body structure of most cancers and chemotherapy-affected organs and tissues, ultrasound imaging is also used. Real-time commentary of fluctuations in blood arteries, lymph nodes as well as organs is feasible with this non-invasive method. Ultrasound helps in estimating the effect of remedy on the immune system by using recognizing

indicators of fluid buildup, infection, or other immune-associated reactions (Chiorean et al., 2016). Additionally, Table 2 provides a description of the strategies for comparing the effect of chemotherapy on the immune system.

CLINICAL OUTCOMES

Chemotherapy has the potential to alter the immune system within and outside of the tumor by converting the tumor microenvironment. Certain chemotherapy drugs have the capability to increase immunological activation, while others can inhibit the immune system (Galluzzi et al., 2020). The body's capacity to generate a defense against different cancerous reactions is impacted via these alterations, which also impair the immune cell configuration in the tumor. Chemotherapy's impact on the immune system emphasizes the significance of understanding the body's drug mechanisms (Wargo et al., 2015).

The immune system can be activated by most chemotherapeutic medicines, particularly those that have an effect on the immune system. For instance, a few drugs such as anthracyclines and platinum-based medications can cause the most cancer cells to die in a way that triggers the immune system to respond strongly towards the tumor. This releases signals that stimulate the immune cells to fight the cancer efficiently (Terenzi et al., 2016). Chemotherapy boosts our immune system's potential to kill cancer cells. It brings specialized immune modulators inclusive of T cells and NK cells to the tumor location. Understanding how chemotherapy activates these immune responses is important which allows us to harness chemotherapy's capacity to construct immunity towards tumors (Duan, 2018). Chemotherapy can weaken the immune- system, reducing the potential to fight infections. This compromised protection mechanism might also intrude on treatment effectiveness. A not-unusual chemotherapy impact, neutropenia possesses the ability to lower neutrophil levels the frontline soldiers against bacterial and fungal invaders. During cancer treatment, this heightened infection threat often necessitates dose modifications (Khan et al., 2017).

Chemotherapy can trigger the loss of life of most cancer cells in a manner that exposes unique identifiers, or antigens, on their surface. This allows the spark off immune cells which include dendritic cells, which play a vital position in beginning and regulating the body's immune reaction against different cancers. The effectiveness of this antigen presentation is a key thing that affects the immune system's potential to understand and target cancer cells (Radogna & Diederich, 2018). Changes purposed by chemotherapeutic drugs can adjust how the body gives antigens, boosting the activation of cytotoxic T cells and triggering an extra powerful immune reaction towards the tumor (Fabian et al., 2021). Tumor-infiltrating lymphocytes (TILs) are immune cells that have entered the tumor environment. They suggest the potential of the body's immune reaction in against cancer. The range of these TILs can provide vital clues for the patient's diagnosis. Chemotherapy treatments can affect the TILs, altering their composition and function. Different studies show that patients with higher numbers of activated T cells tend to have a higher diagnosis (Savas et al., 2016).

Immune checkpoint inhibitors, a class of immunotherapeutic agents, have developed cancer treatment by modulating the immune system to target cancer cells. The combination of chemotherapy with immune checkpoint inhibitors has shown synergistic effects in certain cancers. Chemotherapy-induced release of tumor antigens can enhance the efficacy of immune checkpoint inhibitors by providing more targets for immune recognition (Lehouritis et al., 2015). This combination approach highlights the potential for modulating chemotherapy-induced immune changes to maximize the benefits of immunotherapy, leading to improved treatment responses and long-term outcomes (Pusuluri et al., 2019). Furthermore, while chemotherapy can initially stimulate immune responses, the tumor may develop adaptive resistance mechanisms to evade immune surveillance. This phenomenon is characterized by changes in the tumor microenvironment that impair immune responses, promoting tumor survival (Mohme et al., 2017).

IMMUNE SYSTEM MODULATION STRATEGIES

Patients who receive chemotherapy combined with immunotherapy are expected to have enhanced immune systems that can attack cancerous cells effectively (Ribas & Wolchok, 2018). Furthermore, immune therapy with immune checkpoint inhibitors, monoclonal antibodies, and adoptive cell therapies work on the utilization of the body's immune system to enhance the targeting of tumors. The combination of this therapy with chemotherapy can help to control the immunomodulatory effects induced by the chemotherapy to enhance the immune system response to tumors (Chacon et al., 2016).

This is another way of modulating the immune system during chemotherapy where cytokines the signaling molecules of the immune system are adjusted in terms of their levels and activity to affect immune responsiveness (Sideras et al., 2014). There are specific cytokines incorporating IL-2, IL-12, interferons, and GM-CSF which are capable of eliciting immune responses. These cytokines are given along with the chemotherapy regimen to promote the recruitment of immune cells as well as enhance the overall immunity that fights the tumor (Bhattacharya et al., 2015).

The vaccines that are intended to induce an immune response to particular tumor-associated antigens can be incorporated into therapeutic approaches as complementary therapies to chemotherapy. These vaccines are designed to stimulate the immune system to single out cancer cells much more easily (Tagliamonte et al., 2014). Immunotherapy of mutated tumor associated antigens can be done through dendritic cell vaccines or peptide-based vaccines that stimulate the immune system to get activated for the specific targeted tumor associated antigen. Using these approaches alongside chemotherapy also helps in boosting the immune system's ability to identify and annihilate cancer cells (Najafi & Mortezaee, 2023).

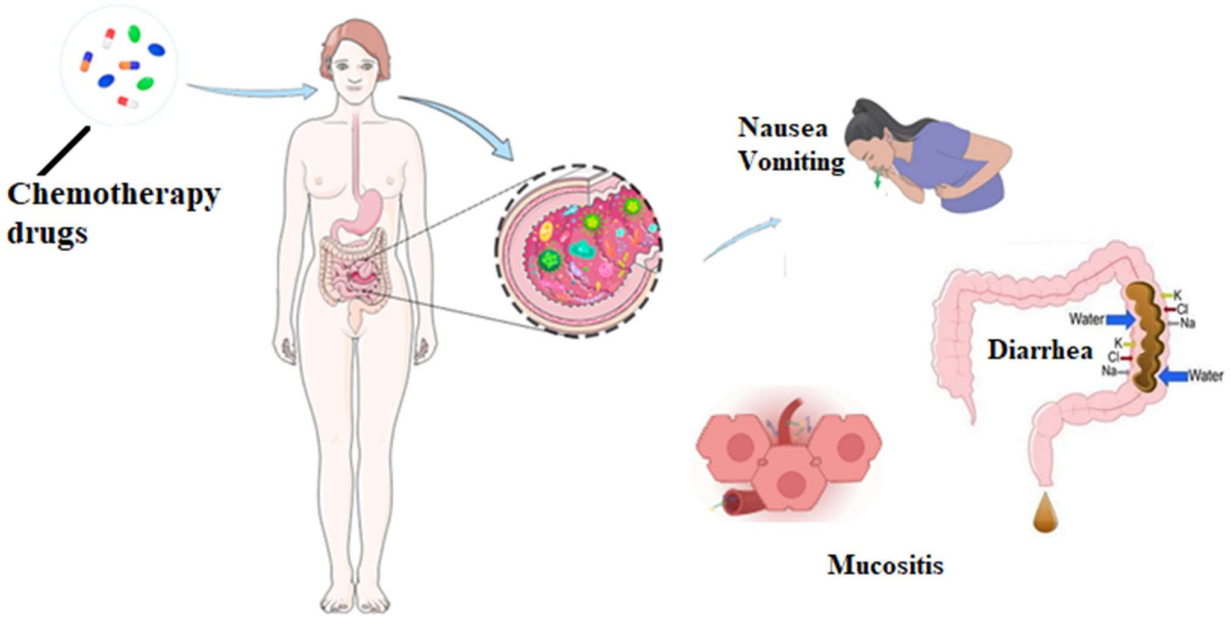

Fig 2. Chemotherapy induced gastrointestinal side effects

Table 1. Interaction between chemotherapy and immune system

Chemotherapy Agent	Immune System Effects	Clinical Implications
Cytotoxic Drugs	Suppresses immune cell proliferation	Increased susceptibility to infections
Immunomodulatory Agents	Modulates immune response	Potential for enhancing anti-tumor immunity
Combination Therapies	Balances cytotoxicity and immune activation	Optimizing treatment efficacy
Immune Checkpoint Inhibitors	Enhances immune activity	Synergistic effects with chemotherapy

Table 2. Techniques for assessing the impact of chemotherapy on the immune system.

Assessment Technique	Function	Advantages
Flow Cytometry	Analyzes individual cells for surface markers	Provides detailed information on cell types
ELISA	Measures concentration of specific proteins	Quantitative assessment of immune factors
Immunohistochemistry	Visualizes distribution of immune components	Allows localization within tissues
Cytokine Profiling	Measures levels of signaling molecules	Reveals immune system activation patterns

Adaptive cell therapies are the methods that include the identification, treatment, and reintroduction of the immune system's cells intended to increase their ability to fight cancer (Stock et al., 2019). For instance, Chimeric antigen receptor (CAR) T-cell therapy is a therapy that entails engineering T cells to treat cancer by attaching a receptor that identifies cancer cells to the engineered cells. Besides, the integration of chemotherapy along with adoptive cell therapies creates a synergistic effect in which chemotherapy enhances the T-cell infiltration and activity in the tumor space through regulation of the tumor microenvironment. (Pottier et al., 2015).

Moreover, the cytotoxic effects of the chemotherapeutic drugs of changing the composition and the micro diversity of the gut microbiota. Cytotoxic agents, including anthracycline and taxan, have been linked with variations in the composition and density of microbiota. It has been reported that these changes as likely to affect the microbial community, switching the balance between the friendly and the less friendly microorganisms (Aarnoutse et al., 2022). Recent research has indicated that the composition of the gut microbiome also plays a potential role in determining the outcome of chemotherapy treatments. The composition of the multifaceted microbial community, applying certain principles of antagonism appears to enhance the effectiveness of treatment. Particular bacterial strains have been linked to improved therapeutic activity and, at the same time, the low dose toxicity level of some chemotherapeutic agents. (Alexander et al., 2017).

Different studies have elucidated that cancer treatment, in particular chemotherapy, results in the alteration of the flora and fauna within the gastrointestinal tract thereby bringing about dysbiosis (Fig 2). It was shown that cancer patients suffer from dysbiosis which can be linked to gastrointestinal side effects including nausea, diarrhea, and mucositis resulting from chemotherapy (Al-Qadami et al., 2019). Disturbances in the complex mutual relations between the gut microbiota and the host that may underlie these pathologic changes can determine the severity of the side effects and the quality of life of the patient during and after the treatment (Secombe et al., 2019).

Regulation of the immune system through the help of the gut microbiome of the host Organism is a known reservoir of an extensive range of microbial flora that is involved in the regulation of the immune system of the host organism (Bashiardes et al., 2017). Metabolites and microbial byproducts are potent immune effector modulators that may promote or inhibit immune activity. The aforementioned alterations of the microbial composition may in turn affect the immune reaction, thus influencing the regulation of antitumor immune responses and other treatment-associated side effects. Chemotherapeutic agents in certain circumstances can induce immunogenic cancer cell death which is a mechanism that leads to exposure of tumor antigenicity. These antigens are then taken and displayed by other antigen presenting cells including the dendritic cells and this activates T cells (Wang et al., 2018). Specifically, the immune checkpoint control device helps in the activation of adaptive immunity and improves the immune system response to tumor cells. Furthermore, this integration with the insertion of TILs, particularly cytotoxic T cells, into tumor tissues, plays a pivotal role in orchestrating the antitumor response. Certain anti-cancer agents, including anthracyclines, which are some of the chemotherapeutic drugs have been related to enhanced TIL infiltration in tumors (Salgado et al., 2015).

Targeted therapies, designed to interfere with specific signaling pathways involved in cancer cell growth, can have immunomodulatory effects. For instance, the tyrosine kinase inhibitors that selectively target the angiogenic regorafenib pathway affect the tumor microenvironment and the immune cells. Combining targeted drugs and chemotherapy seeks to produce a conjugate treatment strategy with single preliminary goals among shock cancer cells while at the same time enhancing the immune system (Mittal et al., 2014).

Immune checkpoint inhibitors, which include programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors have revolutionized the treatment of cancer. These inhibitors assist in the removal of the brakes on immune responses that otherwise hinder the T cells to identify the cancerous cells and destroy them (Pardoll, 2012). Integrating chemotherapy to immune checkpoint inhibitors seeks to increase the immunogenicity of dying chemotherapy cells hence increasing the susceptibility of these cells to chemotherapy and concurrently promoting long-term anti-tumor immunity (Vargas & Apetoh, 2019).

The disturbance of the gut microbial ecosystem has a remarkable effect on the host immune system which also applies to the cancer treatment process. Microbial metabolites such as short-chain fatty acids, can shape the immunogenomics of self and non-self-interactions and thus impact the equilibrium of inflammatory and anti-inflammatory reactions (Lazar et al., 2018). These changes in the microbiome due to chemotherapy can thus be seen to have rather broad impacts on the host immune system where its ability to control suitable responses to tumors is affected (Viaud et al., 2015).

The microbiome acts as a mediator between chemotherapy and the immune system, influencing treatment efficacy. Specific microbial species have been linked to the metabolism and activation of chemotherapeutic drugs (Alexander et al., 2017). For instance, some types of bacteria are capable of converting prodrugs to their active forms and thereby improving the rate of absorption and effectiveness of chemotherapy among others (Mahato et al., 2011). The microbiome also contributes to the potential reduction or mitigation of complications arising from chemotherapy activities. For instance, chemotherapy may disrupt the microorganisms in the gut contributing to mucositis, a condition characterized by inflammation of the mucous membranes in the gastrointestinal system. Some potential remedies are using probiotics or fecal microbiota transplantation aimed at the prevention of these side effects by regulation of microbiota composition (van Vliet et al., 2010).

Immune checkpoint inhibitors (ICIs) are biological drugs that work through immune regulation and are currently considered a cutting-edge therapy for cancer. These drugs target inhibitory pathways in the immune system, essentially releasing the brakes on immune responses against cancer cells. PI3K/Akt/mTOR inhibitors are among the most frequently used agents; PD-1 inhibitors (e. g. pembrolizumab, nivolumab), CTLA-4 inhibitors (e. g. ipilimumab, tremelimumab) belong to the list of programmed death. When combined with chemotherapy, ICIs can synergistically magnify the immune response that is prompted by chemotherapy-induced tumor death, improving tumor detection and clearance (Das & Johnson, 2019). Monoclonal antibodies, (mAbs) are designed to be attached to exact proteins on the layers of cancer or immune cells or to alter immune reactions (Weiner, 2015). For instance, rituximab is an antibody that binds towards CD20 on B cells and is a therapeutic agent used for B-cell lymphomas. Trastuzumab is used to treat breast cancer cells that have a protein called HER2. It is revealed that monoclonal antibodies work synergistically with chemotherapeutic agents to improve the immune system's capacity to recognize cancer cells and destroy them (Pierpont et al., 2018).

Immunomodulatory drugs (IMiDs), such as thalidomide, lenalidomide, and pomalidomide, have demonstrated immunostimulatory effects in the treatment of hematologic malignancies. These drugs modulate the activity of immune cells and the tumor microenvironment, enhancing antitumor immune responses. The combination of IMiDs with chemotherapy aims to modulate their immunomodulatory properties, potentially improving treatment outcomes and overcoming resistance mechanisms (Vallet et al., 2012). Cytokine modulators, such as IL-2 and interferons, have been explored in combination with chemotherapy to boost immune responses. IL-2, for instance, enhances the proliferation and activity of T cells and NK cells (Sim & Radvanyi, 2014). Administering these cytokines along with chemotherapy aims to create a more favorable immune environment, developing an environment conducive to an enhanced antitumor response (Duan, 2018). Furthermore, Table 3 provides a brief description of chemotherapy and immune system interaction.

Table 3. Immune system modulation strategies

Modulation Strategy	Mechanism	Applications
Immunotherapy	Activates or enhances the immune response	Targeted treatment for specific cancers
Vaccination	Stimulates the immune system against targets	Prophylactic and therapeutic approaches
Adoptive Cell Therapy	Infuses engineered immune cells for therapy	Effective against certain malignancies
Cytokine Therapy	Administers specific cytokines for modulation	Enhances immune response in cancer

CONCLUSION

In conclusion, the relationship between chemotherapy and the immune system poses challenges and opportunities in the treatment of cancer. Chemotherapy, while effective in targeting rapidly dividing cancer cells, exerts complex immunomodulatory effects that can impact the body's natural defenses. The delicate balance between eradicating cancer cells and preserving immune function as well as a combination of chemotherapy with immune checkpoint inhibitors along with other immunotherapies presents a potential way for enhancing antitumor immune responses. Moreover, different strategies to modulate the gut microbiome during chemotherapy emerge as a novel approach, with microbial interventions showing tremendous potential in mitigating side effects and influencing treatment efficacy.

REFERENCES

Aarnoutse R, J Ziemons, LE Hillege et al., 2022. Changes in intestinal microbiota in postmenopausal oestrogen receptor-positive breast cancer patients treated with (neo) adjuvant chemotherapy. NPJ Breast Cancer 8:89. https://doi.org/10.1038/s41523-022-00455-5

Ahlmann M & G Hempel, 2016. The effect of cyclophosphamide on the immune system: Implications for clinical cancer therapy. Cancer Chemotherapy and Pharmacology 78:661-71. https://doi.org/10.1007/s00280-016-3152-1

Akkaya M, K Kwak, SK Pierce, 2020. B cell memory: Building two walls of protection against pathogens. Nature Reviews Immunology 20:229-38. https://doi.org/10.1038/s41577-019-0244-2

Alexander JL, ID Wilson, J Teare et al., 2017. Gut microbiota modulation of chemotherapy efficacy and toxicity. Nature Reviews Gastroenterology and Hepatology 14:356-65. https://doi.org/10.1038/nrgastro.2017.20

Al-Qadami G, YV Sebille, H Le et al., 2019. Gut microbiota: Implications for radiotherapy response and radiotherapy-induced mucositis. Expert Review of Gastroenterology and Hepatology 13:485-96. https://doi.org/10.1080/17474124.2019.1595586

Bashiardes S, T Tuganbaev, S Federici et al., 2017. The microbiome in anti-cancer therapy. Seminars in Immunology 32:74-81. https://doi.org/10.1016/j.smim.2017.04.001

Berns A, Ringborg U, JE Celis, M Heitor et al., 2020. Towards a cancer mission in horizon Europe: Recommendations. Molecular Oncology 14:1589-615. https://doi.org/10.1002/1878-0261.12763

Bhattacharya P, I Budnick, M Singh et al., 2015. Dual role of GM-CSF as a pro-inflammatory and a regulatory cytokine: Implications for immune therapy. Journal of Interferon and Cytokine Research 35:585-99. https://doi.org/10.1089/jir.2014.0149

Chacon JA, K Schutsky & DJ Powell Jr., 2016. The impact of chemotherapy, radiation and epigenetic modifiers in cancer cell expression of immune inhibitory and stimulatory molecules and anti-tumor efficacy. Vaccines 4:43. https://doi.org/10.3390/vaccines4040043

Chiorean L, XW Cui, SA Klein et al., 2016. Clinical value of imaging for lymph nodes evaluation with particular emphasis on ultrasonography. Zeitschrift für Gastroenterologie 54:774-90. https://doi.org/10.1055/s-0042-108656

Cutsem E, HM Verheul, P Flamen et al., 2016. Imaging in colorectal cancer: Progress and challenges for the clinicians. Cancers 8:81. https://doi.org/10.3390/cancers8090081

Das S & DB Johnson., 2019. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. Journal for Immunotherapy of Cancer 7:1. https://doi.org/10.1186/s40425-019-0805-8

Desai S & AK Guddati, 2023. Carcinoembryonic antigen, carbohydrate antigen 19-9, cancer antigen 125, prostate-specific antigen and other cancer markers: A primer on commonly used cancer markers. World Journal of Oncology 14:4. https://doi.org/10.14740/wjon1425

Doig K, B Zhang, 2017. A methodical approach to interpreting the red blood cell parameters of the complete blood count. American Society for Clinical Laboratory Science 30:173-85. https://doi.org/10.29074/ascls.30.3.173

Duan H, 2018. Novel therapeutic strategies for solid tumor based on body's intrinsic antitumor immune system. Cellular Physiology and Biochemistry 47:441-57. https://doi.org/10.1159/000489979

Ebersole JL, CL Graves, OA Gonzalez et al., 2016. Dawson III D, Morford LA, Huja PE, Hartsfield Jr JK, Huja SS, Pandruvada S, Wallet SM. Aging, inflammation, immunity and periodontal disease. Periodontology 72:54-75. https://doi.org/10.1111/prd.12135

Fabian KP, B Wolfson, JW Hodge, 2021. From immunogenic cell death to immunogenic modulation: Select chemotherapy regimens induce a spectrum of immune-enhancing activities in the tumor microenvironment. Frontiers in Oncology 11:728018. https://doi.org/10.3389/fonc.2021.728018

Feng SS & S Chien, 2003. Chemotherapeutic engineering: Application and further development of chemical engineering principles for chemotherapy of cancer and other diseases. Chemical Engineering Science 58:4087-114. https://doi.org/10.1016/S0009-2509(03)00234-3

Galli F, JV Aguilera, B Palermo et al., 2020. Relevance of immune cell and tumor microenvironment imaging in the new era of immunotherapy. Journal of Experimental and Clinical Cancer Research 39:1-21. https://doi.org/10.1186/s13046-020-01586-y

Galluzzi L, J Humeau, A Buqué et al., 2020. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. Nature Reviews Clinical Oncology 17:725-41. https://doi.org/10.1038/s41571-020-0413-z

Gun SY, SW Lee, JL Sieow et al., 2019. Targeting immune cells for cancer therapy. Redox Biology 25:101174. https://doi.org/10.1016/j.redox.2019.101174

Hendry S, R Salgado, T Gevaert et al., 2017. Assessing tumor infiltrating lymphocytes in solid tumors: A practical review for pathologists and proposal for a standardized method from the International Immuno-Oncology Biomarkers Working Group: Part 1: Assessing the host immune response, TILs in invasive breast carcinoma and ductal carcinoma in situ, metastatic tumor deposits and areas for further research. Advances in Anatomic Pathology. 24:235. https://doi.org/10.1097/PAP.0000000000000162

Hood L, M Flores, 2012. A personal view on systems medicine and the emergence of proactive P4 medicine: Predictive, preventive, personalized and participatory. New Biotechnology 29:613-24. https://doi.org/10.1016/j.nbt.2012.03.004

Irigaray P, JA Newby, R Clapp et al., 2007. Lifestyle-related factors and environmental agents causing cancer: An overview. Biomedicine AND Pharmacotherapy 61:640-58. https://doi.org/10.1016/j.biopha.2007.10.006

Jin P, J Li, Y Meng et al., 2021. PET/CT metabolic patterns in systemic immune activation: A new perspective on the assessment of immunotherapy response and efficacy. Cancer Letters 520:91-9. https://doi.org/10.1016/j.canlet.2021.06.028

José RJ, JN Periselneris, JS Brown, 2020. Opportunistic bacterial, viral and fungal infections of the lung. Medicine 48:366-72. https://doi.org/10.1016/j.mpmed.2020.03.006

Kartikasari AE, CS Huertas, A Mitchell et al., 2021. Tumor-induced inflammatory cytokines and the emerging diagnostic devices for cancer detection and prognosis. Frontiers in Oncology 11:692142. https://doi.org/10.3389/fonc.2021.692142

Khan Z, XZ Shen, EA Bernstein et al., 2017. Angiotensin-converting enzyme enhances the oxidative response and bactericidal activity of neutrophils. Blood 130:328-39. https://doi.org/10.1182/blood-2016-11-752006

Kratz A, SH Lee, G Zini et al., 2019. International Council for Standardization in Haematology. Digital morphology analyzers in hematology: ICSH

review and recommendations. International Journal of Laboratory Hematology 41:437-47. https://doi.org/10.1111/ijlh.13042
Kuter DJ, 2015. Managing thrombocytopenia associated with cancer chemotherapy. Oncology 29:282.
Lazar V, LM Ditu, GG Pircalabioru et al., 2018. Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. Frontiers in Immunology 9:1830. https://doi.org/10.3389/fimmu.2018.01830
Lehouritis P, J Cummins, M Stanton et al., 2015. Local bacteria affect the efficacy of chemotherapeutic drugs. Scientific Reports 5:14554. https://doi.org/10.1038/srep14554
Lewis DY, D Soloviev, KM Brindle, 2015. Imaging tumor metabolism using positron emission tomography. Cancer Journal 21:129. https://doi.org/10.1097/PPO.0000000000000105
Mahato R, W Tai, K Cheng, 2011. Prodrugs for improving tumor targetability and efficiency. Advanced Drug Delivery Reviews 63:659-70. https://doi.org/10.1016/j.addr.2011.02.002
Mancuso S, M Mattana, M Carlisi et al., 2022. Effects of B-cell lymphoma on the immune system and immune recovery after treatment: The paradigm of targeted therapy. International Journal of Molecular Sciences 23:3368. https://doi.org/10.3390/ijms23063368
Mao S, X Ou, D Zhu et al., 2016. Development and evaluation of indirect ELISAs for the detection of IgG, IgM and IgA1 against duck hepatitis A virus 1. Journal of Virological Methods 237:79-85. https://doi.org/10.1016/j.jviromet.2016.08.019
McKinnon KM, 2018. Flow cytometry: An overview. Current Protocols in Immunology 120:5-1. https://doi.org/10.1002/cpim.40
Mittal K, J Ebos & B Rini, 2014. Angiogenesis and the tumor microenvironment: vascular endothelial growth factor and beyond. Seminars in Oncology 41:235-51. https://doi.org/10.1053/j.seminoncol.2014.02.007
Mohme M, S Riethdorf & K Pantel, 2017. Circulating and disseminated tumour cells-mechanisms of immune surveillance and escape. Nature Reviews Clinical Oncology 14:155-67. https://doi.org/10.1038/nrclinonc.2016.144
Mollaei M, ZM Hassan, F Khorshidi et al., 2021. Chemotherapeutic drugs: Cell death-and resistance-related signaling pathways. Are they really as smart as the tumor cells?. Translational Oncology 14:101056. https://doi.org/10.1016/j.tranon.2021.101056
Najafi S & K Mortezaee, 2023. Advances in dendritic cell vaccination therapy of cancer. Biomedicine and Pharmacotherapy 164:114954. https://doi.org/10.1016/j.biopha.2023.114954
Pardoll DM, 2012. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer 12:252-64. https://doi.org/10.1038/nrc3239
Pierpont TM, CB Limper, KL Richards, 2018. Past, present, and future of rituximab-the world's first oncology monoclonal antibody therapy. Frontiers in Oncology 8:163. https://doi.org/10.3389/fonc.2018.00163
Pottier C, A Wheatherspoon, P Roncarati et al., 2015. The importance of the tumor microenvironment in the therapeutic management of cancer. Expert Review of Anticancer Therapy 15:943-54. https://doi.org/10.1586/14737140.2015.1059279
Pusuluri A, D Wu & S Mitragotri, 2019. Immunological consequences of chemotherapy: Single drugs, combination therapies and nanoparticle-based treatments. Journal of Controlled Release 305:130-54. https://doi.org/10.1016/j.jconrel.2019.04.020
Radogna F & M Diederich, 2018. Stress-induced cellular responses in immunogenic cell death: Implications for cancer immunotherapy. Biochemical Pharmacology 153:12-23. https://doi.org/10.1016/j.bcp.2018.02.006
Rapoport BL, T Cooksley, DB Johnson et al., 2021. Treatment of infections in cancer patients: An update from the neutropenia, infection and myelosuppression study group of the Multinational Association for Supportive Care in Cancer (MASCC). Expert Review of Clinical Pharmacology 14:295-313. https://doi.org/10.1080/17512433.2021.1884067
Ribas A & JD Wolchok, 2018. Cancer immunotherapy using checkpoint blockade. Science 359:1350-5. https://doi.org/10.1126/science.aar4060
Salgado R, C Denkert, S Demaria et al., 2015. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Annals of Oncology 26:259-71. https://doi.org/10.1093/annonc/mdu450
Savas P, R Salgado, C Denkert et al., 2016. Clinical relevance of host immunity in breast cancer: From TILs to the clinic. Nature Reviews Clinical Oncology 13:228-41. https://doi.org/10.1038/nrclinonc.2015.215
Schirrmacher V, 2019. From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment. International Journal of Oncology 54:407-19. https://doi.org/10.3892/ijo.2018.4661
Secombe KR, JK Coller, RJ Gibson et al., 2019. The bidirectional interaction of the gut microbiome and the innate immune system: Implications for chemotherapy-induced gastrointestinal toxicity. International Journal of Cancer 144:2365-76. https://doi.org/10.1002/ijc.31836
Sharma A, S Jasrotia & A Kumar, 2023. Effects of Chemotherapy on the Immune System: Implications for Cancer Treatment and Patient Outcomes. Naunyn-Schmiedeberg's Archives of Pharmacology 31:1-6.
Sideras K, H Braat, J Kwekkeboom et al., 2014. Role of the immune system in pancreatic cancer progression and immune modulating treatment strategies. Cancer Treatment Reviews 40:513-22. https://doi.org/10.1016/j.ctrv.2013.11.005
Sim GC & L Radvanyi, 2014. The IL-2 cytokine family in cancer immunotherapy. Cytokine and Growth Factor Reviews 25:377-90. https://doi.org/10.1016/j.cytogfr.2014.07.018
Spadi R, F Brusa, A Ponzetti et al., 2016. Current therapeutic strategies for advanced pancreatic cancer: A review for clinicians. World Journal of Clinical Oncology 7:27. https://doi.org/10.5306/wjco.v7.i1.27
Stock S, M Schmitt & L Sellner, 2019. Optimizing manufacturing protocols of chimeric antigen receptor T cells for improved anticancer immunotherapy. International Journal of Molecular Sciences 20:6223. https://doi.org/10.3390/ijms20246223
Szczęch J, D Samotij, VP Werth et al., 2017. Trigger factors of cutaneous lupus erythematosus: A review of current literature. Lupus 26:791-807. https://doi.org/10.1177/0961203317691369
Tagliamonte M, A Petrizzo, ML Tornesello et al., 2014. Antigen-specific vaccines for cancer treatment. Human Vaccines and Immunotherapeutics 10:3332-46. https://doi.org/10.4161/21645515.2014.973317
Teoh F & N Pavelka, 2016. How chemotherapy increases the risk of systemic candidiasis in cancer patients: Current paradigm and future directions. Pathogens 5:6. https://doi.org/10.3390/pathogens5010006
Terenzi A, Pirker C, BK Keppler etal., 2016. Anticancer metal drugs and immunogenic cell death. Journal of Inorganic Biochemistry 165:71-9. https://doi.org/10.1016/j.jinorgbio.2016.06.021
Tran AP, MA Al-Radhawi, I Kareva et al., 2020. Delicate balances in cancer chemotherapy: Modeling immune recruitment and emergence of systemic drug resistance. Frontiers in Immunology 11:1376. https://doi.org/10.3389/fimmu.2020.01376
Truong NT, T Gargett, MP Brown et al., 2021. Effects of chemotherapy agents on circulating leukocyte populations: Potential implications for the success of CAR-T cell therapies. Cancers 3:2225. https://doi.org/10.3390/cancers13092225
Vallet S, M Witzens-Harig, D Jaeger et al., 2012. Update on immunomodulatory drugs (IMiDs) in hematologic and solid malignancies. Expert Opinion on Pharmacotherapy 13:473-94. https://doi.org/10.1517/14656566.2012.656091
van Vliet MJ, HJ Harmsen, ES de Bont et al., 2010. The role of intestinal microbiota in the development and severity of chemotherapy-induced mucositis. PLoS Pathogens 6:e1000879. https://doi.org/10.1371/journal.ppat.1000879
Vargas TR & L Apetoh, 2019. Can immunogenic chemotherapies relieve cancer cell resistance to immune checkpoint inhibitors?. Frontiers in Immunology 10:1181. https://doi.org/10.3389/fimmu.2019.01181
Vazquez MI, J Catalan-Dibene & A Zlotnik, 2015. B cells responses and cytokine production are regulated by their immune microenvironment. Cytokine 74:318-26. https://doi.org/10.1016/j.cyto.2015.02.007
Vermaelen K, 2019. Vaccine strategies to improve anti-cancer cellular immune responses. Frontiers in immunology 10:8. https://doi.org/10.3389/fimmu.2019.00008
Viaud S, R Daillere, IG Boneca et al., 2015. Gut microbiome and anticancer immune response: Really hot Sh* t!. Cell Death and Differentiation 22:199-214. https://doi.org/10.1038/cdd.2014.56
Wang YJ, R Fletcher, J Yu et al., 2018. Immunogenic effects of chemotherapy-induced tumor cell death. Genes and Diseases 5:194-203. https://doi.org/10.1016/j.gendis.2018.05.003
Wargo JA, A Reuben, ZA Cooper et al., 2015. Immune effects of chemotherapy, radiation, and targeted therapy and opportunities for combination with immunotherapy. Seminars in oncology 42:601-16. https://doi.org/10.1053/j.seminoncol.2015.05.007
Weiner GJ, 2015. Building better monoclonal antibody-based therapeutics. Nature Reviews Cancer 15:361-70. https://doi.org/10.1038/nrc3930
Yuan J, G Lo, AD King, 2016. Functional magnetic resonance imaging techniques and their development for radiation therapy planning and

monitoring in the head and neck cancers. Quantitative Imaging in Medicine and Surgery 6:430. https://doi.org/10.21037/qims.2016.06.11

Zahorec R, 2021. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratisl Lek Listy 122:474-88. https://doi.org/10.4149/BLL_2021_078

Zhang J, XY Wu, RM Jin, 2022. Neutropenia: diagnosis and management. World Journal of Pediatrics 18:771-7. https://doi.org/10.1007/s12519-022-00593-7

Zingoni A, C Fionda, C Borrelli et al., 2017. Natural killer cell response to chemotherapy-stressed cancer cells: role in tumor immunosurveillance. Frontiers in Immunology8:1194. https://doi.org/10.3389/fimmu.2017.01194