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Article

Chemotherapy-Induced Modulation of Rheumatoid Arthritis Activity in Oncology Patients: A Narrative Review

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by synovial inflammation and progressive joint destruction. In patients with concomitant malignancies, chemotherapy represents a unique immunomodulatory intervention that may significantly influence RA disease activity. This narrative review aims to summarize and critically evaluate current evidence regarding chemotherapy-induced modulation of rheumatoid arthritis activity in oncology patients. Available clinical and experimental data suggest that several chemotherapeutic agents exert profound effects on immune regulation, cytokine production, and lymphocyte proliferation, mechanisms that overlap with the immunopathogenesis of RA. Conventional cytotoxic drugs such as methotrexate, cyclophosphamide, and platinum-based agents have been reported to induce partial remission or attenuation of RA symptoms in some patients, primarily through suppression of autoreactive T and B cells. Conversely, immune checkpoint inhibitors and certain targeted therapies may exacerbate RA activity or trigger immune-related adverse events resembling inflammatory arthritis. The review highlights the dual and context-dependent nature of chemotherapy on RA, influenced by cancer type, therapeutic regimen, baseline autoimmune activity, and patient-specific immunogenetic factors. Changes in inflammatory biomarkers, including tumor necrosis factor-α, interleukin-6, and C-reactive protein, are discussed as potential indicators of chemotherapy-associated shifts in RA disease activity. Additionally, the clinical challenges of differentiating chemotherapy-related arthralgia from true RA flare are addressed. Understanding the complex interaction between chemotherapeutic agents and autoimmune pathways is essential for optimizing clinical management, minimizing adverse outcomes, and improving quality of life in oncology patients with RA. Further prospective studies are warranted to establish evidence-based guidelines for integrated oncologic and rheumatologic care.

Keywords: Rheumatoid arthritis; Chemotherapy; Autoimmune modulation; Inflammatory cytokines; Oncology patients

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1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease of chronic character with persistent inflammation of synovia, progressive destruction of the joints, and extra-

articular manifestations in the individuals when the disease is not responding efficiently to straightforward interventions, treatment is problematic, and in the individuals with the disease, it may be so intractable, as to be scarcely treatable in some way [1,2]. The application of chemotherapy is mainly in the treatment of malignancy and its effects are seen through inhibition of cells that divide fast including the immune cells. Chemotherapy can affect the rheumatoid arthritis activity because of its immunosuppressive and immunomodulatory effect. The article review is a summary of the existing evidence on the impact of chemotherapy on the disease activity of rheumatoid arthritis [3].

People with rheumatoid arthritis (RA) have a much higher chance of dying after being diagnosed with cancer, even though their average cancer incidence rate (CIR) is lower than the general hospitalized population. This was found in a long-term population study of Western Australia. As part of the study, hospital data from thirty years ago were looked at to see if there was a link between cancer and RA. The Western Australia Hospital Morbidity Data Collection, the Cancer Registry, and the Death Registry gave the experts the data they needed. They looked at information on 14,041 people with RA and 33,785 people who were not diagnosed with RA. The researchers found that RA patients were less likely to have had cancer in the past than controls (7.6% vs. 14.2%, $P < 0.01$) [5]. New cancer cases were lower in people with RA (19.68 vs. 24.77 cases per 1,000 person-years), and the incidence rate ratio (IRR) was 0.79. These people had never had cancer before. During the 30-year study, this trend stayed the same. Even though the chance of getting cancer was lower, RA patients were more likely to get lung cancer (IRR 1.17) and blood cancer (IRR 1.21). Also, once a person was diagnosed with RA, their life span was much lower than that of people who did not have RA (median survival: 3.3 years vs. 5.3 years, $P < 0.001$). Most types of cancer were linked to higher death rates, which shows that RA may make the health effects of cancer worse [6].

The data suggest that even though RA patients may not get cancer very often, their outlook is not good once they have been diagnosed with cancer. This shows that RA patients need better cancer screening and care in order to get diagnosed early and get better treatment after diagnosis [7].

Some chemotherapeutic agents have immunosuppressive properties, and these could reduce the transient activity of rheumatoid arthritis (RA) disease since they inhibit the growth of immune cells. Nonetheless, this dual immunomodulatory property requires close clinical observation especially when anticancer chemotherapy is used in combination with RA treatments [8]. Many experts say that people who take disease-modifying antirheumatic drugs (DMARDs) or mainly biologic agents should briefly stop taking them or lower their dose in order to lower their risk of severe immunosuppression, cytopenias, and opportunistic infections. Even with these precautions, patients with RA receiving chemotherapy are still at risk of serious bacterial, viral, and fungal infections, hematologic toxicity such as anemia, leukopenia, and thrombocytopenia among others and slowed wound healing [9]. Chemotherapy can also aggravate fatigue, generalized weakness, joint pain, functional limitations and can also add to the psychological and physical pain. Consequently, regular checking in the laboratories in addition to preventive measures is a part and parcel of patient management. However, with the help of an adequate cancer treatment, long-term prognosis and the quality of life can significantly be improved, which highlights the significance of a multipolar and multidisciplinary approach towards care [10,11].

Rheumatoid arthritis (RA) is an autoimmune inflammatory chronic disease that is linked to immune dysregulation and chronic immunosuppressive therapy. RA patients are also at a disturbed risk of malignancy and might necessitate anticancer chemotherapy as their disease progresses [12]. Morbidity of RA and cancer raises a complicated clinical situation because immunosuppression as a result of chemotherapy can create a synergistic effect with the underlying autoimmune disease and its management. Although more progress has been made in oncology and rheumatology, there is still a lack of integrated

recommendations in how the RA patients without cancer chemotherapy should be managed best. The issue of the risk of infection, disease flare, drug interactions, as well as treatment related toxicity, tends to complicate the clinical decision-making process [13]. Thus, the overall analysis of the presented evidence is needed to determine the clinical consequences, safety issues, and treatment results of anticancer chemotherapy in rheumatoid arthritis patients [14,15].

When someone is weak, a series of complex autoimmune and inflammatory events lead to synovitis, swelling, and damage in the joints that are typical of active RA. They are brought on by parts of both the innate and adaptive immune systems. The enzyme peptidylarginine deiminase changes the arginine residues to citrulline residues after translation, which is how these proteins are made [16]. Because they share epitopes, citrullinated peptides are made. The immune system no longer recognizes these as its own, so it makes ACPAs to fight them. MRI and synovial biopsy data of healthy people were compared to MRI and synovial biopsy data of people with RF and/or ACPA. This showed that systemic autoantibody production happens before inflammation and the formation of adhesion molecules in the synovium. In order for the synovium to become active in RA, this means that it may need that something else happen. A study of 79 people with RA found that RF and ACPA started an average of 4.5 years before the synovial RA [17].

When white blood cells get into the synovium, they cause synovitis. There isn't any local cell division that causes the inflammation of leukocytes in the synovium. Instead, adhesion molecules and chemokines released by busy endothelial cells in microvessels send the white blood cells back to where they came from, which is far away [18]. The swollen synovium doesn't have enough oxygen because the cells there are growing and blood flow is slowing down in the synovial vessels because the synovium is gaining more fluid. More hypoxia causes more angiogenesis in the synovium. This is likely because it starts making factors like vascular endothelial growth factor that help blood vessels form [19].

It's pretty complicated how the immune system gets activated and how RA gets worse because it involves both the adaptive immune system and the natural immune system. The cytokines and chemokines in the synovium where these exchanges happen have a big effect on them. When RA is very bad, the synovial membrane is full of different kinds of inflammatory cells that work together to destroy the joints [20].

The adaptive immune system is important for RA because it is home to dendritic cells, which are a major type of antigen-presenting cell. These cells release a variety of cytokines, HLA class II molecules, and costimulatory molecules in the synovium, which is surrounded by T cell groups. In the synovium, dendritic cells bring antigens to T cells and are also a part of the process by which T cells become activated [21]. T cells must get two messages in order to work. The first clear sign is that antigens are being shown to the T-cell receptor. The costimulatory signal is the second signal that the antigen-presenting (dendritic) cell's protein CD80/86 needs to link with the T cell's protein CD28. When CD80/86 is competitively suppressed, T-cells can't activate, which stops what comes next. The fact that stopping CD80/86 works well as a treatment for RA supports the idea that T cells play a big part in building up RA [22,23].

T-cells were activated and then split into three main subpopulations, each with its own set of actions and cytokines. For a long time, people thought that RA was caused by a Th1 mediator. However, the Th17 subpopulation has been getting more attention recently. Change-promoting factor 2 is released by both dendritic cells and macrophages, along with IL-1, IL-6, IL-21, and IL-23. These chemicals help Th17 cells differentiate and stop regulatory T cells from forming. This changes the synovium's homeostatic reaction to one of inflammation [24,25]. Th17 makes interferon-g, IL-17A, IL-17F, IL-22, IL-26, the chemokine CCL20, and the transcription factor ROR-g. Additionally, fibroblast-like synoviocytes (FLSs) and macrophage-like synoviocytes make IL-17A, which triggers the production of IL-26 and allows monocytes to make the inflammatory cytokines IL-1b, IL-

6, and TNF-a. IL-17A can also play a role in inflammatory responses through antigen-nonspecific pathways, which are set off when activated T cells interact with macrophages and fibroblasts [26,27].

And finally, humoral adaptive immunity is also a big part of how RA happens. There are different ways that B cells can play a role in autoimmune diseases. If the body isn't able to check the tolerance of B cells well, antireactive B-cells can form. These are antigen-presenting cells that can activate T cells [28]. It is also possible for B cells to make cytokines that either promote or inhibit inflammation. Not only that, but B cells can also make antibodies. Each of these processes can play a part in how RA starts, or they can work together.30. The fact that drugs that get rid of certain types of B cells have been shown to help control RA is more proof that these cells play a role in the disease. Based on clinical trials, rituximab, a monoclonal antibody against B cells that are CD20 positive, has been shown to be successful in RA. It is now approved as a treatment for RA patients who have not responded to TNF inhibitors [29,30].

NK cells, such as macrophages, mast cells, and natural killer cells, make it up. Neutrophils, on the other hand, may be found in joint fluid. The body has many kinds of cells, and each kind has its own macrophages. These have a lot to do with synovitis and the immune and inflammatory reaction. When they come into contact with an immunogenic trigger, like a microbial pathogen, they do this by phagocytosis, antigen presentation, and the release of pro-inflammatory cytokines, reactive oxygen intermediates, prostanoids, and matrix-degrading enzymes [30]. Proinflammatory cytokines are quickly released when TLRs are activated. Neutrophils, monocytes, and lymphocytes are drawn in, which helps the immune system fight off the infection. It is processed antigen that macrophages and dendritic cells pick up and move through peripheral lymphoid tissue. There, they show antigen to cells of the adaptive immune system. Because of this, cells respond and antibodies are made. Most of the time, the innate and adaptive immune systems kill pathogens when they work together. This process is known as annexation of the immune response. The inflammatory reaction does not go away, though, once the pathogens are gone from the RA environment. Instead, it stays active in a chronic state [31,32].

How RA starts and spreads is also affected by signaling routes inside cells. Several types of cytokines, chemokines, antibodies, and antigens that cause inflammation bind to receptors on the outside of certain cells [33]. It is common for receptor binding to start a chain of signaling events inside the cell. These events finally reach the cell's nucleus and change gene expression, which can affect how the cell works. Most of the time, changes in how immune cells show their genes are connected to how they make and release inflammatory chemicals when they sense a threat [34]. When they are released into the extracellular environment, they change or boost the original signal. The intercellular signaling pathways are made up of the STAT pathway, the spleen tyrosine kinase (Syk) pathway, the Janus kinases (JAK) pathway, the mitogen-activated protein kinase (MAPK) pathway, and the nuclear factor k-light-chain enhancer of activated B cells (NF-kB) pathway. Multiple pathways can talk to each other, as described [35].

Immune systems need intracellular signaling pathways to work right, and changes in these pathways that are caused by androgens may lead to autoimmune diseases.There is a first group of small chemicals that are used to treat RA right now. These molecules work against intracellular targets. These lines are likely to be looked into even more, and more therapeutic targets will be found. Inflammation in RA is also linked to normal changes in mesenchymal tissue. When someone has RA, the FLSs that live in the synovium multiply and change into a different type.9 IL-6, TNF, interferon-g, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1 are just some of the inflammatory mediators and adhesion molecules that are released when FLSs and T cells come into touch with each other in an inflamed synovium. When FLSs are bent, they break down joint tissue by releasing a group of proteases that damage the joints [36,37].

Rheumatoid arthritis (RA) is an autoimmune disorder that is manifested by inflammation of joints. The autoantibodies in the serum of RA patients have given numerous leads to the disease pathophysiology [38]. Researchers have found that RA can be further divided into two types based on the presence of certain autoantibodies. These include rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), anti-carbamylated protein antibodies (anti-CarP), and more recently, anti-acetylated protein antibodies [39]. Genetic and environmental factors that make people more likely to get RA, like certain human leukocyte antigen (HLA) genes and smoking, are linked to the development of these autoantibodies. It is possible to detect autoantibodies many years before the onset of the disease in a sub-group of patients and this indicates that there are a series of processes that lead to the initial formation of autoantibodies in predisposed hosts, which is followed by an inflammatory reaction that results in clinically apparent arthritis [40,41]. Studies of the nature and the effecter mechanism of these autoantibodies could shed some light in the pathophysiological mechanisms that lead to arthritis in RA. According to recent statistics, ACPA may contribute to the continuation of inflammation, having developed. Moreover, pathophysiological pathways have been identified that can prove the existence of direct interactions between the existence of ACPA and bone erosions as well as pain in patients with RA. Finally, exploring the potential pathogenic quality of autoantibodies can result in a better comprehension of the underlying pathophysiological mechanism in rheumatoid arthritis [42,43].

TNF-a, IL-1b, and IL-6 are pro-inflammatory cytokines that are central in the control of the inflammation and innate immune response. Activated macrophages and other immune cells primarily produce them as a response to infection or tissue damage. TNF-alpha brings about endothelial mobilization, adhesion molecules expression, recruitment of leucocytes to inflammatory foci, fever, and activation of the acute-phase response; excessive production may result in septic shock. When expressed chronically, IL-1b is a potent fever mediator, T-cell activator, vascular permeability, and inflammatory signaling amplifier, which leads to tissue damage [44,45]. The role of IL-6 includes the induction of hepatic production of acute-phase proteins, including C-reactive protein, the differentiation of B-cells into plasma cells, and the connection of innate and adaptive immune systems. These cytokines all have a synergistic effect in enhancing inflammatory responses, orchestrating body-wide effect e.g. fever, production of acute-phase proteins, and play a role in the pathogenesis of chronic inflammatory and autoimmune diseases when they become dysregulated [46].

There is also a link between rheumatoid arthritis (RA) and the HLA-DRB1 genes that code for a five-amino-acid sequence motif at the 70–74 positions of the HLA-DRB2 chain. This sequence motif is called shared epitope (SE) [47]. No one knows how the SE-RA relationship is based on mechanisms. Not long ago, we found that the SE works as an allele-specific signal transducing ligand that activates a nitric oxide (NO)-mediated pathway in other cells. In order to get a better idea of what the SE does in the immune system, we've talked about how it affects the activation of T cells in mice [48]. The SE decreased the activity of the enzyme indoleamine 2,3 dioxygenase (IDO), which was a key player in immune tolerance and T cell control in CD11c+CD8+ dendritic cells (DCs). On the other hand, the ligand increased the production of IL-6 in CD11c+CD8− DCs [49]. When SE-activated DCs and CD4+ T cells were cultured together, they stopped Foxp3+ T regulatory (Treg) cells from differentiating and made Th17 cells bigger. These polarizing effects were seen with SE-positive synthetic peptides, but they were stronger when the SE was found in its natural three-dimensional form as part of HLA-DR tetrameric proteins. Injecting SE ligand into living things increased the number of Th17 cells in lymph nodes that drain lymph nodes and the production of IL-17 by splenocytes [50,51]. So, we can say that SE is a strong immune-stimulating ligand; it can change T cells into Th17 cells, which are a type of T cell that has recently been linked to the development of inflammatory diseases like RA [52].

2. Materials and Methods

Surgery Chemotherapy is a form of treatment that involves the use of drugs to attempt to prevent the growth of cancer or even killing the cancerous cells. Chemotherapy kill cancer cells by inhibiting their multiplication unlike a surgery or radiation therapy which is sometimes unable to penetrate metastases spread throughout the body [53].

Several drugs that are meant to fight cancer are currently being tested in human trials. Some of them are from well-known groups of cancer drugs, while others are the first of a new family of drugs. We think that clinicians should keep the key groups in mind, which is why we propose a classification based on goals. The target could be in the tumor cell itself or in other parts that come into touch with the tumor cells, such as the immune system, host cells, or the endothelium [54].

The fundamental processes of chemotherapy include 1) the deterrence of the appearance of drug-resistant Mycobacterium tuberculosis, 2) the bactericidal effect of medications, and 3) the principles of intermittent dosage of medication. Since the advent of streptomycin in 1947, prevention of drug resistance development has been the primary objective of developing drug regimens. Later on, more efforts have been given to strategies of enhancing the effectiveness of health care administration and patient adherence. This would be achieved through reduction of chemotherapy period or administration of the drugs under full surveillance and intermittently. It is critical to the nature of the bactericidal activity of antibacterial drugs in the interpretation of short course chemotherapy; intermittent drug dosage has its theoretical side [55].

There are many ways that chemotherapeutic drugs are used in clinical medicine to treat conditions where the goal is to weaken the immune system of the host. Immunosuppression is used in medicine to treat immunologically driven diseases, lymphoproliferative diseases, and graft rejection. There are five types of agents that can be used for this purpose: ionizing radiation, corticosteroids, antilymphocyte sera and antimetabolites, and biological alkylating agents. It is known how each drug affects a certain molecular process, but it is not so clear how they affect the cellular events of immune reactions. One of the side effects of chemotherapy is a weaker immune system. This makes the body more likely to get opportunistic infections or cancer [56]. It talks about the different parts of humoral and cellular defense and gives specific examples of how to keep an eye on them. Immunologic studies of immunologic immunodeficiency in lymphoma patients and heart transplant patients taking immunosuppressant drugs have shown that these groups of patients have selective deficiencies in cell-mediated immunity to herpes viruses, which may make them more likely to get infected by these viruses [57].

Chronic inflammation is also associated with the pathophysiology and disease pathogenesis of rheumatoid arthritis (RA). The most prevalent metastatic form of advanced prostate cancer among the elderly is prostate cancer with bone metastasis (PCa-BM), which can result in significant changes to the prognosis and the quality of life of the patients despite the use of chemotherapy, the chronic inflammation that occurs may increase the risk of joint injuries further to cause RA and other complications. Thus, the investigation of the risk of developing chronic inflammation due to chemotherapy in the risk of RA in PCa-BM patients is of crucial significance, Chemotherapy significantly provoked the development of inflammatory factors into the tumor microenvironment of PCa-BM. Inflammatory biomarkers such as TNF- 2, IL- 6, IL- 10, IL- 17 A, and p-STAT3 were elevated. These were inflammatory cytokines induced by chemotherapy, which was related to RA and significantly reduced with the process of anti-inflammatory intervention [58].

The manifestation of chemotherapy-related rheumatic disease is different in different patients regarding when the conditions present themselves, the kinds of symptoms and the outcome of the manifestation after treatment. Enlightenment of this negative side effect is likely to bear a number of fruits. There would be a possible reduction in the number of unnecessary investigations by health care providers. Besides this, the

level of anxiety among the patients would be reduced by educating them on the chances of developing rheumatic symptoms after chemotherapy. Lastly, more reporting of the incidence of this side effect with chemotherapy will aid in the determination of the real incidence and prevalence of the side effect [59].

complex underlying motive in which physical, psychological and environmental influences had impacts on the physical activity in early rheumatoid arthritis patients. To develop more effective health interventions, one should take into consideration the complexity of practicing physical activity, and person-centred approach can be taken into account. The person-centred approach should consider factors like physical considerations, economics and time to undertake physical activities [60].

3. Results

Out Cytokines also mediate a wide spectrum of inflammatory mechanisms that are involved in the pathogenesis of rheumatoid arthritis. In rheumatoid joints, it is not a secret that an imbalance of pro and anti inflammatory cytokine functions is predisposed to the development of autoimmunity, chronic inflammation and hence joint destruction. Nevertheless, less understandable is the manner in which cytokines are also structured in a hierarchical regulatory system and, as a consequence, which cytokines might be the most appropriate cytokines to be targeted in clinical interventions in rheumatoid synovitis [61,62]. The acute phase response raises the levels of proteins that are part of the complement system, the clotting and fibrinolytic systems, antiproteins, transportation proteins, and other proteins that are involved in the inflammatory response, such as IL-1Ra [63]. These proteins are made by hepatocytes in reaction to IL-6 and other cytokines that are released during infections, cancer, and both short-term and long-term inflammatory diseases. Acute-phase proteins are mostly anti-inflammatory, but IL-6 and other proteins in its family, such as IL-11, can be either pro-inflammatory or anti-inflammatory. RA has other effects on the body that are caused by IL-1 and TNFa, such as fever, tiredness, muscle pain, muscle damage, and weight loss [64].

Different cytokines, chemokines, angiogenic, and growth factors could be released by human tumor cell types. Luminex multiplex technology was used to study this. The media that had been changed by the tumor protected tumor cells from drugs that cause apoptosis and helped the tumor cells grow. The antibodies that blocked IL-6, CXCL8, CCL2, and CCL5 stopped this activation. When doxorubicin and cisplatin were given to tumor cells, they caused a big rise in the release of VEGF, IL-6, CXCL8, CCL2, and G-CSF. It was found that this stimulation caused NF-akB, AP-1, AP-2, CREB, HIF-1, STAT-1, STAT-3, STAT-5, and ATF-2 transcription factors to become active. It also caused gene expression for IL-6, CXCL8, FGF-2, CSF-3, and CCL5 to rise. When doxorubicin and anti-G-CSF, anti-CCL2, or CCL5 neutral antibodies were used to treat tumor cells, they had a stronger blocking effect than when they were used alone [65,66]. These results show that the chemokines and growth factors that tumors release by attaching to specific receptors on stroma and tumor cells may be signals that help tumors grow and stop drugs from killing them. Using antibodies that block VEGF (Avastin/Bevacizumab) or inhibitors of the HER2/neu signal (Herceptin/Trastuzumab) with chemotherapy has been shown to make it work better, but only in some cases. Drugs that cause the production of growth and proangiogenic factors may cancel out the benefits of antibody therapy [67]. Also, a lot of growth factors and chemokines have effects that promote growth and blood vessel formation, so decreasing just one factor is not enough to stop tumor growth completely. So, a general interaction with the tumor cytokine network is needed to make cancer treatment even more effective [68].

Chemotherapy is the mainstay of cancer treatment, and it is also known to result in immune suppression, which can also carry serious consequences on the outcome of the patient. The purpose of writing this review paper is to provide a broad overview on the influence of chemotherapy on the immune system and its influence on cancer treatment.

Chemotherapy may have direct impact on immune cells resulting in cytotoxic effects, cell differentiation, changes in cell functions, and interference with cell communication and signaling pathways. This immune suppressive effect may undermine the anti-tumor immune response and cause immune related toxicity risk. Gaining a better insight into the processes that lead to immune suppression during chemotherapy is essential in order to maximize the treatment plan [69]. The measures that can be put to prevent immune suppression are use of immunomodulatory agents as adjuvants to chemotherapy; combination therapy to boost the immune system and supportive care of the immune system. Moreover, the discovery of possible biomarkers to anticipate immune suppression and inform decisions on treatment is a promising future of personal cancer therapy. The future directions of the same field include the further clarification of the underlying mechanisms, the new combination therapy, and the targeted interventions to reduce immune suppression. This knowledge of chemotherapy-induced immune suppression and its treatment can be applied to improve the efficacy of cancer treatment, augment anti-tumor immune response, and improve patient outcome [70,71].

Risks of Immunosuppression TNF inhibitors, methotrexate, and other non-biological and biological DMARDs in the treatment of rheumatoid arthritis (RA) may worsen the immune system of cancer patients and expose them to an increased risk of infections and, potentially, of tumor proliferation. Consequently, they are forced to be halted in the process of chemotherapy. Synergistic Antitumor Effects: Recent research has proposed that certain combinations such as the use of an antirheumatic drug, auranofin, with anticancer drugs may enhance the killing of cancer cells, which may lead to the possibility of enhancing efficacy in treatment [72]. Shared used agents include methotrexate used in both disciplines, although at much higher dosages in the treatment of cancers like breast cancer, leukemia, and lymphoma, and at much lower dosages in the treatment of RA. Indirectly caused by chemotherapy: Rheumatism may result because of chemotherapy and it must be addressed with caution, often using RA drugs like sulfasalazine or methotrexate. Monitoring and Management: Infection and liver damage (e.g. with the use of methotrexate) may require strict monitoring in patients, and immune checkpoint inhibitors (ICIs) have to be managed since they can lead to autoimmune disease and the oncology and rheumatology specialists should monitor all these treatments together [73,74].

Disease-modifying anti-rheumatic drugs (DMARDs) are medications that exhibit disclosing action in the treatment of the inflammatory joint illness, especially RA. These medications slow down the destruction of the joints and decrease the immune activities which lead to pain and inflammations. An agent is said to be diseasemodifying in case it has been shown to stop or slow the damage of the joints in RA in radiographic images of hands or feet .DMARDs are divided into two broad groups, which are conventional and biologic DMARDs. Traditional DMARD is represented by medications like methotrexate and hydroxychloroquine, but biologic DMARD can be monoclonal antibodies or soluble receptors [75]. This category of medications is slow-moving and requires several weeks before they affect. Typical representatives of traditional DMARDs are methotrexate, hydroxychloroquine, azathioprine, sulfasalazine, leflunomide, cyclosporine, gold salts, D-penicillamine, and tetracycline. Methotrexate is employed in RA, in monotherapy and combination treatment with the DMARDs or biologic agents. It is also more survivable in comparison to other DMARDs. Methotrexate suppresses the disease progression better than other DMARDs.Methotrexate suppresses cell proliferation, and enhances T-cell apoptosis [76,77].

Targeted synthetic DMARDs and biologic agents are important agents in the management of rheumatoid arthritis that selectively inhibit inflammatory pathways like TNF-C, IL-6, B-cell stimulation, and JAK-STAT signals. In chemotherapy patients with cancer, they can be used to control the activity of RA, but can also impair immune response and cause immune complications. To find the right compromise between effective cancer

treatment and effective control on the activity of rheumatoid arthritis, a meticulous timing, a dose variant, and close multidisciplinary monitoring are necessary [78].

When chemotherapy is used in the treatment of oncology patients with rheumatoid arthritis in combination with DMARDs, close safety monitoring is necessary as there is some overlap in toxicities and immunosuppression. The most important ones are severe infections, cytopenias, hepatotoxicity (particularly in the case of methotrexate and leflunomide) and renal dysfunction which can change the drug clearance. Opportunistic infections risk may be further enhanced by concomitant corticosteroids and biologics whereas NSAIDs may enhance bleeding and renal toxicity during chemotherapy. Periodic CBC, liver and renal checks, screening of the latent infections, vaccination planning and oncology-rheumatology joint decision-making are all necessary [79,80].

Arthritis and arthralgia following chemotherapy of lung cancer are not rare conceiving after chemotherapy. The musculoskeletal pain that occurs post-chemotherapy may have negative impacts on the quality of life but are not often life-threatening. The post-chemotherapy arthritis and arthralgia should be characterized in terms of pattern, severity, and treatment, which will aid in turning it into a well-known phenomenon. This will simplify its differentiation with metastatic disease, expedite correct diagnosis without unnecessary investigations, it will also allow early establishment of proper therapy and as a result reduce patient anxiety and more so improve their quality of life [81,82].

The manifestations of chemotherapy induced rheumatic disease differ in patients regarding the time of presentation, the nature of the manifestations and prognosis after the treatment. Heightened awareness about this negative side effect will probably yield a number of advantages. The cases of unwarranted investigations by the health care givers would also be reduced. Moreover, the training of patients with the risk of the onset of rheumatic symptoms after chemotherapy would probably decrease their anxiety. Lastly, enhanced reporting of the incidence of this side effect, which comes with chemotherapy, will aid in determining the actual incidence and prevalence of the side effect [83,84].

The process of differential diagnosis between a Rheumatoid Arthritis (RA) flare and an arthritis caused by drugs depends on time and whether the person has a history of specific medications, the presence of autoantibodies, and treatment responsiveness. RA is characterized by systemic inflammation and high titer antibodies whereas drug-induced arthritis tends to clear up soon after the withdrawal of the aggressive drug. The most important diagnostic instruments are a detailed review of medications, serology, and imaging [85].

The outcome of a broad range of tumour-derived biologic mediators, which include hormones, peptides, antibodies, cytotoxic lymphocytes, autocrine and paracrine mediators, lead to paraneoplastic symptoms caused by a malignancy but nevertheless not directly linked to tumour invasion. Paraneoplastic syndromes should be recognized and this may result in the early diagnosis of cancer. Conversely, the levels of clinical severity of the symptoms may be a predictor of the degree of response to underlying tumour treatment [86,87]. This influences the quality of life of the patient hence the importance of palliative treatment of paraneoplasia is very high.Malignancy can be manifested musculoskeletally and either accompany or precede the discovery of cancer, or predict its recurrence. The disease progresses in a way that is similar to the primary tumor, and when the primary cancer is cured, the rheumatic disorder generally goes away too. Knowing that some cancer signs don't mean the cancer has spread is helpful for finding and treating a hidden tumor early on. Some rheumatic symptoms that could mean there is a cancer underneath are unusual arthritis with clubbing or widespread bone pains in a patient aged 50 or more, persistent vasculitis that can't be explained, refractory fasciitis, Raynaud's syndrome that doesn't respond to vasodilators, rapidly progressive digital gangrene, or Lambert Eaton myasthenic syndrome. As part of treatment, the cancer must be controlled, and the rheumatic syndrome must be treated with non-steroidal anti-inflammatory meds or corticosteroids to ease the symptoms [88,89].

4. Conclusion

The process of chemotherapy is triggered by multifaceted and context-dependent rheumatoid arthritis activity in cancer patients. Although some chemotherapeutic agents can be immunosuppressive and inhibit autoimmune inflammation temporarily, some treatments especially those that stimulate immunity can make symptoms of rheumatoid worse or cause an immune reaction. The effect is dependent on the nature of malignancy, the chemotherapy therapy used, the underlying activity of RA, and the presence of disease-modifying antirheumatic drugs. Comorbidity between cancer and RA has serious clinical issues, such as predisposition to infections, hematological toxicities, and impaired functioning. Consequently, tailored care plans, clinical follow up, and periodic laboratory examinations need to be applied to maintain patient safety. The use of multidisciplinary teamwork between oncologists and rheumatologists is essential in trying to balance between effective cancer treatment and the appropriate management of rheumatoid arthritis. More prospective studies are necessary in the future to provide standardized clinical guidelines and enhance long-term outcomes and quality of life of this complicated population of patients.

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