Application of cytokines in the treatment of breast cancer

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Abstract. Breast cancer is one of the most common cancers in women globally. Breast cancer is still a major public health issue despite great advancements in diagnosis and treatment. In 2020, there will be about 2.3 million new cases of breast cancer, including about 600,000 deaths. In China, breast cancer is the most common cancer among women aged 15-44, and its mortality rate is on the rise. In recent years, researchers have focused on using cytokines as a potential therapy for breast cancer. Small proteins known as cytokines are essential in the immune system's response to cancer cells. This article discusses the current state of research on using cytokines to treat breast cancer. Specifically, it explores four methods of cytokine therapy: interferon therapy, tumor necrosis factor therapy, interleukin therapy, and colony-stimulating factor therapy. The article also examines the experimental evidence supporting the use of these therapies in treating breast cancer. Overall, this research suggests that cytokine therapy may hold promise as a new approach to treating breast cancer.

Keywords: Breast cancer; Cytokines; Therapy Interferon.

1. Introduction

Breast cancer is a malignant tumor that often develops from cells inside the breast. It can infect nearby tissues and organs and spread to other parts of the body through metastases. Breast cancer is a physiologically and clinically complex illness with a variety of identified histotypes and molecular subtypes, each with a unique etiology, risk factor profile, treatment response, and prognosis [1].

Invasive carcinoma of the breast, not otherwise specified (NOS, also known as ductal carcinoma; 70%–75%) and lobular carcinoma (12%–15%) are the most prevalent histological tumor forms. Additionally, there are 18 additional uncommon subtypes that make up 0.5% to 5% of all breast tumors [2]. The symptoms of breast cancer include: Breast lump or thickening, nipple discharge or bleeding, redness or skin dimpling of the breast skin, wrinkling or indentation of the breast skin, enlarged or hardened lymph nodes in the breast area.

As the most prevalent cancer diagnosed globally, female breast cancer has surpassed lung cancer. In 2020, there were an anticipated 2.3 million new instances of breast cancer, representing 11.7% of all cancer cases, and 684,996 cases of the disease resulted in death. In comparison to transitioned nations, transitional countries showed considerably higher mortality rates for female breast cancer (15.0 per 100,000 vs. 12.8 per 100,000) [3]. Breast cancer is the most common cancer among Chinese women, with an estimated 306,000 new cases in 2016. In China, where it was the most common cancer among women between the ages of 15 and 44, breast cancer mortality rates remained on the rise [4].

Interferons, tumor necrosis factors, and other cytokines are examples of the class of proteins known as cytokines that have the ability to control immune system activity. Cytokines are frequently employed in immunotherapy and targeted therapy for the treatment of breast cancer. Some cytokines also assist the tumor in evading immune responses and benefiting from them. Cytokines are significant regulators of tumor growth and metastasis. For instance, TGF- attaches to MDSCs and causes them to inhibit NK cells [5]. At present, there are four common ways to treat breast cancer through cytokines, namely interferon therapy, tumor necrosis factor therapy, interleukin therapy and CSF therapy. Each of them has different treatment mechanism and advantages and disadvantages.

This review introduces the breast cancer and highlight the mechanism of cytokines to cure the breast cancer. The current methods of treating breast cancer by cytokines are compared and analyzed.

2. Interferon therapy

Interferon is a cytokine that can stimulate the immune system (macrophage and T cell activity) to enhance the body's immune response to tumors. In breast cancer treatment, interferon can be used as an immunostimulant to enhance the body's immune system's anti-cancer ability. Interferon can stimulate immune cells in the body to produce interferon-gamma (IFN-gamma), thereby enhancing the body's killing effect on tumor cells. In addition, interferon can inhibit the proliferation and metastasis of tumor cells and promote tumor cell apoptosis. Studies have shown that interferon therapy can enhance the body's immune response to tumors, improve treatment efficacy, inhibit the proliferation and metastasis of tumor cells, promote tumor cell apoptosis, and when used in combination with other drugs, it can have a synergistic effect and improve treatment efficacy. The IFN pathway plays a crucial role in tumor development, including value-added, differentiation, and metastasis. Studies have demonstrated that inhibiting the IFN pathway can lead to tumor cell death. Recently, a clinical trial investigating the treatment effect of interferon α-2b in breast cancer patients showed that interferon α-2b significantly improves patient survival rates and prognosis while reducing tumor recurrence rates. Interferon therapy is essential for breast cancer as it stimulates the immune system to clear breast cancer tumor cells. The anti-tumor (hIFNα-2b) gene is located on chromosome 9, encoding a 19 Kda protein, with a gene size of 495bp and no introns. The interferon α-2b protein is a type of glycoprotein called "cytokines" that activate cell signaling pathways in response to the presence of viruses, bacteria, parasites, etc., when bound to cell-specific receptors. The hIFNα-2b gene promotes the immune system to defend against tumor suppression. The American Cancer Society (ACS) conducted significant interferon trials in 1978, producing interferon α in 1986, which was then approved for hairy cell leukemia. In cancer patients receiving radiation therapy, researchers have identified mutations in cancer-fighting, antiviral, and defense-control genes, including the hINFα-2b gene sequence, which lead to changes in the hINFα-2b protein. There are 32% (hIFNα-2b) gene mutations, all of which are frameshift mutations. Studies on post-radiation genetics have identified single nucleotide polymorphisms (SNPs) associated with radiation response and their impact on gene expression. Genetic variation plays an important role in radiation response. Radiation can induce lymphocyte depletion and changes in T and B cell distribution, impairing the immune system of these patients, which can hinder treatment. Certain cell types (such as "lymphocytes") can tolerate cell apoptosis during irradiation. The complete blood cell count (CBC) is evaluated to verify the immune response inhibition or alteration of cancer disease and radiotherapy treatment in cancer patients. A study group evaluated immune capacity by lymphocyte count, delayed hypersensitivity skin testing, and in vitro responses of blood lymphocytes from breast cancer patients treated with curative breast surgery to phytohemagglutinin. The conclusion was that locally irradiated patients had a higher level of immune suppression than those who did not receive radiation therapy after breast surgery. Another study investigated the effects of interferon β -1a on breast cancer cells and showed that interferon β -1a could act by inhibiting the proliferation of breast cancer cells and promoting the apoptosis of tumor cells. Related studies looking into interferon's impact on breast cancer cells have revealed that by triggering the immune system, interferon can prevent breast cancer cells from proliferating and encourage them to undergo apoptosis. Another experiment explored the effects of interferon treatment on breast cancer stem cells, and the results showed that interferon can act by inhibiting the proliferation and promoting the differentiation of breast cancer stem cells [6]. However, interferon itself has certain toxic side effects, such as fever, chills, and headaches. In addition, it needs to be used for a long time to achieve the maximum therapeutic effect, resulting in a long treatment cycle. According to surveys, interferon is generally expensive, which brings a certain economic burden to patients.

3. Tumor necrosis factor therapy

TNF is a cytokine that can both indirectly and directly kill tumor cells by causing them to undergo apoptosis. TNF can be used in conjunction with other medications to treat breast cancer, enhancing

their ability to destroy cancer cells through the use of targeted therapeutic strategist (Tumor Necrosis Factor) is thought to cause tumor necrosis when administered in large doses, but it also has a major accelerating effect on tumor growth and plays a variety of roles in angiogenesis, cell invasion and proliferation, and the immune response of the tumor microenvironment [7]. Type II transmembrane proteins in the TNF superfamily are modeled after TNF. They are involved in coagulation, endothelial function, lipid metabolism, and insulin resistance and are secreted by activated macrophages, NK cells, T cells, monocytes, mast cells, fibroblasts, and neurons. TNF signaling is caused by either TNFR1 or TNFR2, one of the two TNF- receptors. The ectodomain of the TNFR1 receptor is shed and internalized when TNF interacts to it. Ectodomain shedding is regulated by plasma membrane matrix metalloprotease, which is followed by proteolysis. Contrarily, pro-apoptotic signaling (mediated by TRADD/FADD/Pro-Caspase-8) or the assembly of Complex I (TRADD/TRAF2/RIP) and the apposition of adaptor molecules to the cell surface occur when the receptor is internalized. Transcription factor activation and MAPK signaling are the next steps. The formation of complex I may lead to the activation of IKK, which causes the ubiquitin-proteasome system to phosphorylate and eliminate IB. As a result, NF-B signaling is stimulated and pro-inflammatory genes are expressed [8]. Research has found that TNF can directly induce apoptosis of tumor cells, inhibit tumor growth and metastasis, and enhance the body's immune response to tumors, improving treatment efficacy. When TNF is used in combination with other drugs, it can have a synergistic effect and improve treatment efficacy. In addition, TNF can stimulate immune cells in the body to produce interferon-gamma (IFN-gamma), enhancing the body's immune response to tumors. Experimental results have shown that TNF therapy has a significant effect on breast cancer treatment. The mTNF-α subtype is capable of reducing tumor growth, and its expression does not affect tumor proliferation or angiogenesis. Tumors expressing mTNF-α lack tumor-associated bone marrow cells, and the soluble factor derived from mTNF-α does not affect the migration of CD11b+ myeloid cells. The non-apoptotic route used by mTNF- to cause cell death is mediated by ROS generation. These test results support the efficacy of TNF treatment in the management of malignancies. TNF- has been identified as a crucial cytokine influencing tumor progression based on data from studies and human cancer. TNF-insufficiency or suppression in animal models lowers the risk of cancer development and may even boost resistance to chemically induced skin carcinogenesis. TNF-expression levels in ovarian cancers have a positive correlation with tumor grade, which is consistent with this. TNF-, on the other hand, also has anti-tumor characteristics. According to the experimental findings, TNF medication may one day be a successful breast cancer treatment [9]. We discovered that TNF enhanced the anticancer effects of the chemotherapy medication paclitaxel while inhibiting the proliferation and migration of breast cancer cells via increasing apoptosis and cell cycle arrest [10]. The combination of TNF and the drug blood can inhibit tumor angiogenesis and promote apoptosis of tumor cells, thus improving the therapeutic effect. In addition, TNF can stimulate the production of interferon- γ (IFN-γ) by immune cells in the body and enhance the body's immune response to tumors. Recent studies have found that TNF increases IFN- γ production in breast cancer patients, indicating an enhanced immune response to tumors. TNF treatment has potential to treating breast cancer by inducing tumor cell apoptosis, inhibiting tumor growth and metastasis, and enhancing the body's immune response to tumors. However, TNF itself has certain toxic side effects, such as fever, chills, and headaches. In addition, TNF has strong biological activity and needs to be precisely controlled during use to avoid overstimulating the immune system and causing adverse reactions. Clinical trials have also shown that TNF has a short half-life in the body, requiring frequent injections to maintain treatment efficacy.

4. Interleukin therapy

Interleukin-2 (IL-2) and Interleukin-12(IL-12) are cytokines that can stimulate the immune system and enhance the body's immune response to tumors. In breast cancer treatment, IL-2 and IL-12 can be used as an immunostimulant to enhance the body's immune system's anti-cancer ability. Studies have shown that IL-2 and 12 can stimulate immune cells in the body to produce IFN-gamma, thereby

enhancing the body's killing effect on tumor cells. In addition, IL-2 and 12 can promote the activation and proliferation of immune cells, enhancing the body's immune system's anti-tumor ability. Interleukin therapy can enhance the body's immune response to tumors, improve treatment efficacy, promote the activation and proliferation of immune cells, enhancing the body's immune system's anti-tumor ability, and when used in combination with other drugs, it can have a synergistic effect and improve treatment efficacy. Clinical investigations to assess IL-2's anticancer activity were started more than 30 years ago, and they were justified by the immunostimulatory capabilities of this cytokine. Since 1992 and 1998, respectively, the FDA has approved the use of high-dose recombinant IL-2 administered intravenously for the treatment of metastatic renal cell carcinoma (RCC) and melanoma. In about 12% of melanoma patients and about 7% of RCC patients, this treatment results in complete responses (CRs), which have a propensity to be long-lasting. Due to IL-2's short (85 minute) half-life, which necessitates 8 hourly doses, and the high frequency of grade 3 adverse events (AEs), like vascular leak syndrome, are drawbacks to utilizing IL-2 clinically. Toxins that harm the heart, etc. Additionally, the immune-suppressive regulatory T (Treg) cells that can inhibit antitumor responses are activated by IL-2. It is primarily the binding of IL-2 to the constitutively generated high-affinity trimeric IL-2 receptor (IL-2R), which is made up of the, and subunits, that causes this effect on Treg cells and the increased risk of vascular leak syndrome. The low-affinity dimeric IL-2 receptor, which is expressed by CD8+ T cells, memory T cells, and NK cells, is devoid of the CD25 component. Medication that selectively activates the immunostimulatory, low-affinity IL-2R complex has been created in an effort to benefit from this variance. For instance, the PEGlyated form of IL-2 called bempegaldesleukin enhances signaling via the subunit (CD122) and preferentially binds to IL-2R, activating CD8+ T cells and NK cells instead of Treg cells. The PEGylation of this substance may also increase the half-life of IL-2 (to around 20 hours) and decrease toxicities related to peripheral blood T cell activation cell and CD8+ T cell proliferation is encouraged by IL-12, which also increases the cytotoxic potential of these cells. In addition, IL-12 improves antigen presentation by promoting the growth of T helper 1 (TH1) cells and IFN production. Due to its robust anti-angiogenic characteristics, IL-12 is a cytokine with therapeutic promise. But like IL-2, the short half-life and toxicity of IL-12 have limited its therapeutic usefulness. Systemic recombinant IL-12 has been used in studies to treat patients with cutaneous T cell lymphoma, non-Hodgkin lymphoma, or RCC. It has also been used as a monotherapy or in combination with other cytokines or vaccines. But significant adverse events (AEs), including fatalities, caused this therapy to be widely abandoned. Despite these problems, systemic IL-12 has been demonstrated to increase CD8+ T cell tumor penetration, at least in melanoma patients [11]. However, IL-2 and 12 themselves have certain toxic side effects, such as fever, chills, and headaches. According to surveys, IL-2 and 12 have strong biological activity and need to be precisely controlled during use to avoid overstimulating the immune system and causing adverse reactions. IL-2 and 12 treatment requires long-term continuous administration, which may affect patients' quality of life.

5. Colony-stimulating factor (CSF) therapy

A cytokine called colony-stimulating factor (CSF) can encourage the growth and differentiation of hematopoietic system cells, encouraging hematopoietic stem cells in the bone marrow to give rise to diverse types of blood cells such platelets, red blood cells, and white blood cells. In breast cancer treatment, CSF is widely used in the treatment of leukopenia, which can alleviate chemotherapy-induced bone marrow suppression and immune suppression by promoting the generation of white blood cells. During chemotherapy or radiotherapy, the patient's hematopoietic system is damaged due to the toxic side effects of these treatments, resulting in leukopenia. White blood cell production can be increased and immune system defense can be strengthened when hematopoietic stem cells are encouraged to proliferate and differentiate. and alleviating chemotherapy-induced bone marrow suppression and immune suppression. Studies have shown that CSF therapy can alleviate chemotherapy-induced bone marrow suppression and immune suppression, reduce the risk of

infection and other adverse reactions, enhance the body's immune system's resistance, enhance the body's resistance to tumors, and increase the number of white blood cells, thereby improving treatment efficacy. Recent studies have explored the effect of a CSF on breast cancer cells. The study used in vitro cell culture to expose breast cancer cells to CSF and observe their effects on cell proliferation and apoptosis. The findings suggested that by enhancing the immune system's reaction, this CSF could prevent breast cancer cells from proliferating and encourage their death. Another experiment investigated the effect of a novel CSF treatment on breast cancer stem cells. The study used a mouse model, in which mice were injected with breast cancer stem cells and treated with different doses of CSF. The results suggest that this therapeutic approach can work by inhibiting the proliferation of breast cancer stem cells and promoting their differentiation. The study discovered that G-CSF stimulates the mTOR signaling pathway, which facilitates the accumulation of MDSC in breast cancer. AKT-mTOR signaling pathway activity increased along with MDSC accumulation, which in turn stimulated G-CSF expression in cancer cells, according to reverse protein array analysis of a breast tumor model. High quantities of G-CSF are expressed by tumor-initiating cells (TIC), and MDSC promotes the expression of stemness-related genes in cancer cells like Nanog, LGR5, and MSI-1. Additionally, MDSC promotes G-CSF enhancement and consequently increases MDSC accumulation by activating the Notch signaling pathway, which in turn drives TIC performance enhancement. This creates a positive feedback loop between TIC and MDSC. Significant tumor growth was significantly slowed in mice given the mTOR inhibitor rapamycin. These findings suggest that the mTOR/G-CSF/MDSC signaling pathway controls the development of breast cancers that are malignant. The pro-angiogenic factor Bv 8 protein is further promoted, Ly 6 G + Ly 6 C + granulocytes (a subset of CD11b + Gr 1 + cells) are more prevalent in organ-specific metastatic sites, and breast tumor metastasis is enhanced by G-CSF released by tumors. In a breast cancer model, anti-G-CSF therapy greatly reduced lung metastases. The establishment of a metastatic niche is aided by the hypoxic tumor microenvironment. The transcriptional pathways mediated by hypoxia-inducible factor (HIF) -1 and -2, which mediate adaptive responses in the cells when exposed to the hypoxic milieu, activate breast carcinoma cells. It first established a connection between the pulmonary metastasis of breast cancer and the CAIX-NF-B-G-CSF cell signaling axis. HIF-1 activation dramatically boosts the expression of CAIX in breast cancer under hypoxic conditions.NF-B activation in the microenvironment is necessary for CAIX expression and the G-CSF-driven migration of granulocytic MDSC to the breast cancer-derived lung metastatic niche. Even with 100% depletion of CAIX, constitutive NF- B activation can restore normal G-CSF secretion. The mobilized G-CSF-dependent granulocyte MDSC can promote the growth and proliferation of disseminated tumor cells as well as the development of lung metastases through immunosuppression [12]. However, CSF treatment requires long-term injection, which may increase the risk of infection and other adverse reactions. CSF treatment may cause excessive white blood cells, leading to an overactive immune response. In experiments, CSF treatment may increase treatment costs.

6. Challenge and improvement

Currently, cytokine therapy is used to treat breast cancer, including interferon therapy, tumor necrosis factor therapy, interleukin therapy, and colony-stimulating factor therapy. However, these therapies face limitations and challenges. Interferon therapy is essential for breast cancer as it stimulates the immune system to clear breast cancer tumor cells. However, the use of interferon therapy is limited by its side effects, including flu-like symptoms, fever, and fatigue. Additionally, some patients may develop antibodies to interferon, which can reduce its effectiveness. Tumor necrosis factor therapy has been used to treat breast cancer by inducing tumor cell death. However, the use of this therapy is limited by its toxicity and side effects, including fever, fatigue, and muscle pain. Interleukin therapy has been used to treat breast cancer by activating the immune system to attack cancer cells. However, the use of this therapy is limited by its side effects, including fever, fatigue, and pain. Colony-stimulating factor therapy has been used to treat breast cancer by increasing

the production of white blood cells. However, the use of this therapy is limited by its side effects, including bone pain and flu-like symptoms.

Despite these limitations and challenges, cytokine therapy remains a promising treatment option for breast cancer. Future research is needed to develop more effective and less toxic cytokine therapies. Additionally, new strategies are needed to overcome the challenges of cytokine therapy, such as developing targeted delivery systems that can deliver cytokines directly to cancer cells while minimizing their toxicity to healthy cells.

7. Conclusion

In conclusion, cytokine therapy is a promising treatment option for breast cancer. By leveraging the role of cytokines in the immune response against cancer cells, researchers hope to develop targeted and effective therapies that can improve patient outcomes. Interferon therapy targets tumor cell proliferation and enhances immune system activity, while tumor necrosis factor therapy focuses on inducing apoptosis in cancer cells. Interleukin therapy involves utilizing specific interleukins to modulate the immune response against breast cancer cells. Colony-stimulating factor therapy stimulates the production of immune cells that target cancer cells. However, it is currently limited by its toxicity and side effects. Future research should focus on developing more effective and less toxic cytokine therapies and on overcoming the challenges of cytokine therapy through the development of targeted delivery systems. With continued research and development, cytokine therapy has the potential to become a more effective and less toxic treatment option for breast cancer patients.

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