Cytokines in Cancer Immunotherapy

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Abstract: Cytokine immunotherapy is a widely concerned field in cancer treatment. As proteins of the immune system, cytokines can regulate the immune response of the host to tumor cells and directly induce tumor cell death. However, there are some limitations in the treatment of cytokines. On the one hand, low dose single drug therapy of cytokines has no significant therapeutic effect; on the other hand, high dose therapy may cause a variety of side effects due to the pleiotropic effect of cytokines. The involvement of cytokines in pro-tumor and anti-tumor immune responses remains an urgent issue. This article mainly introduces the application of cytokines in cancer treatment. Although the efficacy of early stage cytokines in cancer treatment is modest, advances in molecular biology and genomics are expected to optimize and enhance cytokine therapy in clinical practice in the future.

1 INTRODUCTION

Cancer immunotherapy is one of the most effective ways to help the immune system recognize and fight cancer cells (Conlon, K. C. et al. 2019). Cytokines promote the function of the immune system in cell signaling.

Autocrine is where cytokines act on the mother cell that secretes them, while paracrine is where cytokines may act on nearby cells. Endocrinology is caused by the action of cytokines on distant cells. The types of cytokines identified include chemokines, interferon (INF), interleukins (ILs), colony stimulating factors (CSFs), tumor necrosis factors (TNFs), transforming growth factors (TGFs), lymphocytokines, and single cytokines. There are also artificially produced interleukins that can be used to treat alder interleukin cancer. These cytokines can be roughly divided into three categories according to their roles and functions. Lymphokines and single cytokines are produced by immune system cells and are involved in various aspects of immune function. The second and third groups include growth factors and colony-stimulating factors, which control tissue growth and blood cell proliferation. Chemokines are produced by chemotactic activity and are involved in the regulation of the immune system. Cytokines act through cell surface receptors and modulate the balance between humoral and cell-mediated immunity. They are produced by a range of cells, including B lymphocytes, T lymphocytes, macrophages, mast cells, endothelial cells, fibroblasts and stromal cells. The cytokines have effects of pleiotropism, which means that one cytokine that binds to different targets can produce different effects. For example, the activated T helper cell can produce IL-4, which can bind to B cells, thymocytes and mast cells. The IL-4 can induce activation, proliferation, and differentiation on B cells. However, it can only induce proliferation on thymocytes and mast cells. Another property of some cytokines is redundancy. Multiple cytokines may have the same effects on the same target. As an example, the activated T helper cell can produce IL-2, IL-4, IL-5 at the same time. If they all bind to the receptor on B lymphocytes, they may induce the same function of proliferation. In addition, some cytokines can influence the activity of other cytokines in different ways, and they can also act synergistically or antagonistically (Zhang, J. M., & An, J. 2007).

In this review, it mainly focused on 5 concepts, including the discovery of cytokine immunotherapy,

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the mechanism of cytokines, interleukins and interferons and their targeted cancer, the current progress and issues of cytokine immunotherapy, and the predicted improvements.

2 THE DISCOVERY OF CYTOKINES

Cytokines play an important role in the diagnosis, prognosis and treatment of human diseases (Dinarello, C. A. 2007). IL-2 was the first cytokine found to have therapeutic effects, significantly stimulating the growth of T cells and natural killer cells (Robert Gallo, M. D. et al. 1976).

IL-2 successfully treated patients with advanced metastatic renal cell carcinoma and melanoma. Currently, researchers are focusing on whether IL-2 is effective in combination with other cytokines in these cancer patients (Jiang, T., Zhou, C., & Ren, S. 2016). IL-7 is a major regulator of T cell homeostasis. The cytokine driven regeneration of T cells was demonstrated in the first human clinical trial using IL-7, and IL-7-based therapies may also restore immune function in other immunocompromised individuals, such as those living with HIV and the elderly, and may enhance the efficacy of vaccines and other cancer immunotherapies (Fry, T. J., & Mackall, C. L. 2002). Similar to IL-2, IL-15 triggers the production of immune cells that attack and kill cancer cells. Results from the first human clinical trial showed that IL-15 significantly increased T and NK cell growth and activity. IL-15 is currently being investigated for its potential to enhance the effectiveness of vaccines against viruses that cause cancer and autoimmune diseases (Mackall, C. L. et al. 2011).

3 MECHANISM OF CYTOKINES

Cytokines help the immune system do its job. Immune cells, cytokines and organs must communicate with each other to prevent pathogens or harmful invaders from entering the body. The first immune cell that notices the pathogen creates and sends out messages in the form of cytokines to the rest of the organs or cells in the body, responding directly. Different types of cytokines will be released into the blood or directly into tissues, and then, locating the immune cells that are designed to target and bind to the cell receptors.

3.1 Jak-STAT Pathway

Cytokines use multiple signaling pathways. One of the pathways is the Jak-STAT pathway which is shown in figure 1.

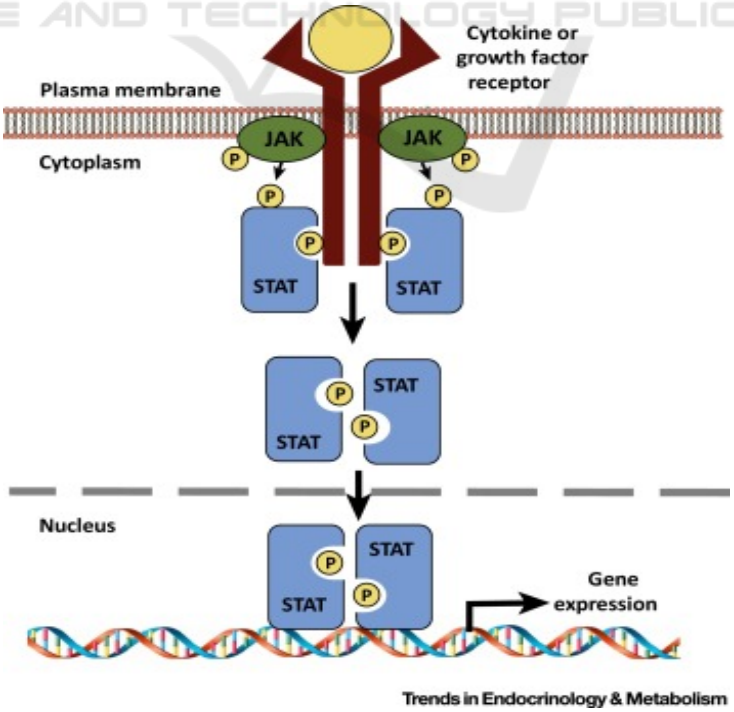

Figure 1: Cytokine signaling through JAK–STAT pathway (Dodington, D. W. et al. 2018).

The Jak-STAT pathway is a very rapid cytosol-to-nuclear signaling pathway, and it involves both Janus kinase protein (JAK) and signaling transducer and activator protein (STAT). Cytokine molecules first bind to the receptors and stabilize heterodimer and bring the JAKs together (Leonard, W. J., & Lin, J. X. 2000). JAK phosphorylates each other which can increase the activity of the tyrosine kinase domain. Activation of JAK kinase in turn phosphorylates the relevant receptor tyrosine residues.

These phosphotyrosines act as docking sites for STAT proteins (Greenlund, A. C. et al. 1995). All STAT share basic features (Darnell, J. E. et al. 1994; Darnell, J. E. 1997), including an N-terminal domain (important for dimer formation), a coiled-coil domain (crucial for dimerization tag and nuclear localization signal), a DNA binding domain (binding to a specific DNA sequence), a linker domain, a SH2 domain (docking STAT to phosphorylated tyrosine residue), and a C-terminal region that contains a critical tyrosine residue and a transactivation domain (Mitchell, T. J., & John, S. 2005). They are then separated from the receptor to form homo-dimer or hetero-dimer after they are recruited (Horvath, C. M., & Darnell, J. E. 1997). The STAT protein is then transferred to the nucleus, where it binds the DNA to the regulatory region of the target gene and regulates gene expression.

3.2 Inflammation

Cytokines mainly occur when the body is invaded by pathogens and cause inflammatory responses by changing the porosity of the blood vessel cell wall and reducing cell contact area. Blood then leaks into surrounding tissue, allowing immune cells to enter the damaged area and begin the healing process (Bio-Rad. n.d.). The inflammatory response, along with physical tissue damage, directs brain cells to release chemicals. Cytokines are essential for a healthy immune response, but the concentrations need to be just right. Too high levels can overwhelm the body, creating a phenomenon known as "cytokine storm." Cytokine storms usually occur when pathogens enter the body at the same time, or when the body mis-produces cytokines early in the immune response. Every organ has cytokine receptors, and in this case, oversignaling helps the immune system precisely clear pathogens. In addition, cytokine storms can have negative effects on the body. Patients with bacterial infections often experience cytokine storms, symptoms of some diseases such as COVID-19. Cytokine storms participate in an uncontrolled immune response that causes a decrease in oxygen in the blood (Ragab, D. et al. 2020). Fluid builds up in the lungs causing breathing difficulties and nervous system problems. The brain is naturally protected from harmful chemicals because of the blood-brain barrier, but the cytokines are so small that they easily cross the brain's protective membrane (Manoylov, M. K. 2020, November 6).

3.3 Network of Pleiotropic Cytokines

The work of different cytokines on different cells can be concluded in figure 2.

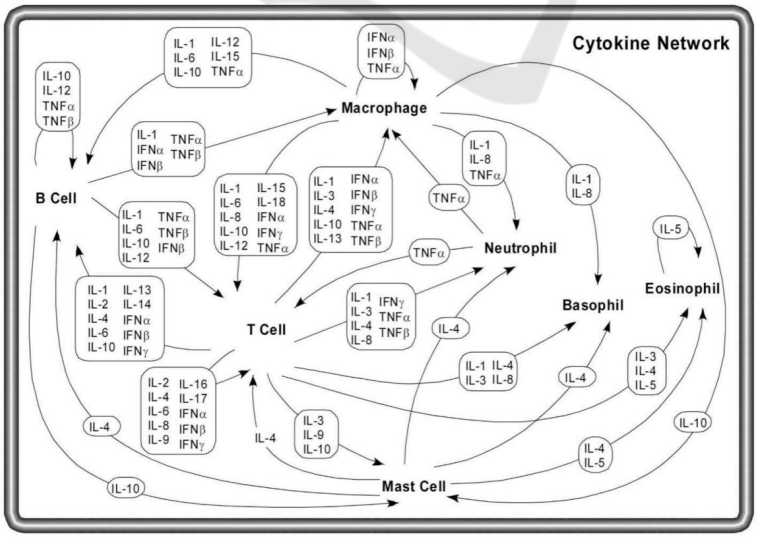

Figure 2: Network of cytokines (Zhang, J.-M., & An, J. 2007).

It shows the paracrine signaling network of different cytokines. Cytokines are pleiotropic, which means that different cells may secrete the same cytokines, and a single cytokine may act on different cells. Cytokines include B cells, T cells, macrophages, mast cells, neutrophils, basophils, and eosinophils. Macrophages engulf foreign cells and present pathogens, use cytokines to stimulate specific immune responses of B cells and T cells, and activate non-specific immune responses produced by other cells (such as natural killer cells). T cells secrete a variety of factors, interferon and interleukin, which participate in the immune response of specific antigens. Proliferation and activation of eosinophils, neutrophils, and basophils also play a role in cytokines. They fight cancer by interfering with cancer cell growth and reproduction, stimulating the immune system, encouraging killer T cells and other cells to attack cancer cells, and encouraging cancer cells to produce chemicals that attract immune cells.

4 INTERLEUKINS AND INTERFERONS

4.1 Interleukins (ILs)

Interleukins are cytokines involved in the regulation of immune response, inflammation and hematopoiesis (Sims, J. E. et al. 1988). A majority of them are produced by macrophages, CD4+ T cells, monocytes and endothelial cells, and bind to their target receptors. They have different effects when they target different target cells.

IL-2 are secreted by T cells (Th1-cells), and target on activated cells, macrophages on their receptors of CD25/IL2RA, CD122/IL2RB, CD132/IL2RG, resulting in a growth and differentiation (Ymer, S. et al. 1985). The source cell of IL-2 includes activated Th cells, mast cells, NK cells, endothelium and eosinophils. The target cells, including hematopoietic stem cells and mast cells, have receptors of CD123/IL3RA, CD131/IL3RB. They will induce the differentiation and proliferation of myeloid progenitor cells, and growth and histamine release of the mast cells (Dorssers, L. et al. 1987).

Other interleukins have different functions by acting on other leukocytes. As one of the basic cytokines with multipotency for the resistant framework, the natural capacity of IL-2 is intervened by IL-2 receptor, which has a place with type I cytokine receptor (Lippitz, B. E. 2013). IL-2 receptor is a trimer complex made of three subunits α, β, γ. Binding of IL-2 to its receptor can induce multiple signaling pathways (STAT, PI3K-Akt and MAPK, three downstream signaling pathways). Activation of IL-2 can promote the growth of immune cells and enhance the activity of immune cells, which can attack and kill cancer cells (Spolski, R. et al. 2018). In the 1990s, high doses of IL-2 were approved for several patients with metastatic melanoma and metastatic renal cell carcinoma and showed long-lasting complete responses. In immunotherapy clinical studies, patients with advanced melanoma and neurocytoma who have responded to high-dose IL-2 therapy have been reported to have prolonged survival of 3-5 years in patients with melanoma and neurocytoma who have responded to high-dose interleukin-2 therapy (Chow, S. et al. 2016). At the same time, low doses of IL-2 can also treat some autoimmune diseases. Low doses of IL-2 may be targeted at the underlying role of Treg cells, leading to the re-control of autoimmune diseases and inflammation (Orozco Valencia, A. et al. 2020). The FDA first approved recombinant IL-2 as effective tumor immunotherapy for patients with cancer. However, severe adverse reactions and priority amplification of immunosuppressed Treg cells limit recombinant IL-2 in cancer therapy. In order to reduce toxicity and prevent the targeting effect of Treg cells, some newly developed fusion proteins can improve the efficacy and lower toxicity of tumor therapy. These include NKTR-214, which has been shown to mask the region of IL-2Rα interaction with its six releasable PEG chains, thereby mediating the preferentially activated effector cells and showing good tolerability and significant clinical activity in patients with advanced melanoma. It is reported that high-dose IL-2 therapy for renal cell carcinoma and metastatic melanoma showed that about 16% of patients reacted emphatically to treatment and the reaction kept going longer in patients with metastatic melanoma (Clark, J. I. et al. 2021). The use of high doses of IL-2 has been associated with severe side effects, such as encephalitis and meningitis. The combination of IL-2 agents with other anticancer immunotherapy agents (such as cell metastasis, antigen-specific vaccines, and cytotoxic T-cell associated antigen 4 can further develop therapy proficiency while lessening IL-2 dosages and diminishing antagonistic occasions (Dhupkar, P., & Gordon, N. 2017). The utilization of IL-2 in malignant growth, intense leukemia, immune system illnesses, human immunodeficiency (HIV) and different infections, among which the therapy of foundational lupus erythematosus (SLE) has gained momentous headway (Orozco Valencia, A. et al.

2020). At present, IL-2 is an effective and safe treatment. However, the toxicity of IL-2 is expected and controllable in clinical medicine. The treatment of IL-2 without treatment-related death can also be applied to inflammatory diseases or autoimmune diseases to improve the therapeutic effect of IL-2-based cytokine. IL-2 therapy can amplify and activate effector T cells and NK cells, providing alternative immunotherapy options for patients following conventional cancer treatment.

4.2 Interferons (IFNs)

There are two main types of interferons: type I interferons (IFN-alpha and IFN-beta), type II interferons (IFN-gamma). Type I interferons are a group of antiviral cytokines. They are induced during viral infections by viral replication products (Eg. double stranded RNA). IFN-alpha is produced by white blood cells except lymphocytes, whereas IFN-beta is produced by fibroblasts. These two kinds of type I interferons are both produced when cells have been infected by pathogens, as a warning signal to the body's immune system. Their main function is to trigger immune cells (including natural killer cells and cytotoxic T lymphocytes) to release type II interferons, also known as IFN-gamma, to fight the germs. The type II IFNs are produced by increasing phagocytosis by macrophages. One common function of these interferons is that they all inhibit viral replication (Katze, M. et al. 2002). IFN-alpha can also be used to treat cancers of hairy cell leukemia, chronic myelogenous leukemia (CML), kidney cancer, melanoma and so on (American Cancer Society n.d.).

In the late 1980s, cytokine-based immunotherapy became the primary treatment for locally advanced or metastatic renal cell carcinoma (RCC) (Koneru, R., & Hotte, S. J. 2009). The antitumor effect is regulated by different mechanisms such as immunomodulation, antiproliferative activity, regulation of gene differentiation, etc. In the randomized controlled trials, patients treated with the IFN-alpha subtype were studied with patients treated with non-IFN-alpha subtypes as a control group. The result demonstrated that the IFN-alpha subtype is related to a more significant remission, indicating a better efficacy than the control group. The IFN-alpha group also had lower 1-year mortality. From the research, there was no difference between the IFN-alpha 2a and 2b subgroups (Coppin, C. et al. 2005). The dose-response effect regarding the IFN-alpha group remained unclear. However, with the increased dose, the toxicity level would be expected to be higher. The dose might be individualized based on the severity and the progress of the disease.

IFN-alpha was also an antitumoral agent common in leukemia; the direct effects include cell growth inhibition, apoptosis induction, enhancement of acute myeloid leukemia (AML). The binding of IFN-alpha regulates these effects to their receptors which can be expressed on the leukemic cell surfaces. The binding can activate specific cell signal pathways, including Jak-STAT pathway activators. Even though people have understood specific pathways were directly related to the leukemia treatment, the precise role of these pathways in AML remained to be researched (Anguille, S. et al. 2011). AML patients can have impaired immune function, and some of their immune responses might not be as intense. Therefore, other indirect effects of IFN involved activating dendritic cells, T cells, and natural killer cells, which played a massive role in antileukemic immune responses. As for other types of leukemia, such as chronic myeloid leukemia (CML), IFN was once the best treatment for CML. However, when tyrosine kinase inhibitors were invented and used, they became the first-line treatment, and interferon is rarely used for CML.

The last class of cancer usually treated IFN-alpha as a single agent was lymphoma. One of the review articles published in 2003 indicated the IFN as a single treatment of cutaneous T-cell lymphoma was efficacious. The IFN was filtered by the glomeruli, and they can undergo fast proteolytic degradations during tubular reabsorption (Olsen, E. A. 2003). One of the problems with the interferon usage in lymphoma patients was the development of the neutralizing antibodies, which might be influenced by the underlying disease, the dosing regimen of cytokine-based immunotherapy, or the duration of the treatment. The presence of the antibody can essentially decrease the efficacy of the medication in lymphoma patients. One of the possible reasons for the development of antibodies can involve the overactive immune response. Therefore, people started to look for other solutions. In 2015, one randomized controlled trial was done to compare the concurrent use of IFN-alpha with low doses of methotrexate or retinoids, which can suppress the immune system. It was found that the use of IFN with retinoids or a low dose of the cytotoxic drug can be preferred in patients with refractory T-cell lymphoma, and the toxicity was minimal for this combination (Aviles, A. et al. 2015).

So far, only these three cancer types were using cytokine-targeted medications for treatment as monotherapy agents, and people have found other solutions with the development of the newer

medication. As for other cancers such as brain tumors and phase 1 and 2 clinical studies of IFN were conducted on patients with malignant brain tumors. People did find some of the patients have shown improved disease states. However, the effect remained in the local area, and it did not show the systemic effect, so it failed to move onto the next stage (Nagai, M., & Arai, T. 1984). Due to the lack of response to monotherapy, people, in general, do not use them. Still, since they are immunomodulators and they can influence the immune response in general, IFN combination with radiotherapy or chemotherapy brought people's interest. People have done an investigation on combination therapy.

5 THE CURRENT PROGRESS AND ISSUE OF CYTOKINES

At the laboratory level, experiments on mice demonstrated that the cytokines had a preclinical effect. Interferon can treat hair cell leukemia and interleukin can treat advanced melanoma and metastatic kidney cancer. IL-12, IL-15, IL-21 and granulocyte macrophage colony stimulating factors have also been used in clinical trials. Despite this, cytokine as a monotherapy did not fulfill its early promise, because parenteral administration of cytokine did not reach sufficient concentrations in tumors. Increased cytokine concentration may indicate an uncontrolled immune response, which is called cytokine release syndrome or cytokine storm. This can lead to severe inflammation, shock, respiratory failure, organ failure, and in some cases even death (Waldmann T. A. 2018).

As previously discussed, cytokine-based therapy indicated antitumor characteristics; people further found the effect was achieved by inhibiting proliferative effects on cells, so tumor cells were not growing as fast. Meanwhile, they also indirectly stimulated our immune system, which can kill tumor cells. Therefore, the mechanism included two perspectives. The first is to decrease cancer cells' growth and increase the immune system to get rid of them. There are multiple cytokines found that have therapeutic effects. However, more specifically for cancer, only IL- 2 and IFN-alpha demonstrated antitumor effects and the FDA approved them for the treatment of cancers. The other cytokines, such as IL-17, can be used for the treatment of autoimmune diseases like psoriasis. Even though the antitumor effects were not as desired due to the low efficacy, they showed better outcomes when using other anticancer agents. The combination therapy showed a more promising effect than the monotherapy.

There are a few barriers related to these medications, and some of them should be further developed. One of the most significant issues with these medications was the low efficacy while having high toxicities. One of the guesses related to the high kidney response and low liver response might relate to the pharmacokinetics of this class of medication. They are mainly renally cleared and the liver clearance was minimal. The major toxicities involved the loss of appetite, high infection risk, flu-like symptoms such as fever, chills, and fatigue. All of these could be very common, and people might see them in patients on cytokine-based immunotherapy. The possible further research can focus on improving pharmacokinetics and pharmacodynamics, improving local reaction instead of a systemic reaction, and optimizing the combination therapy to achieve better outcomes. In general, cancer cells can develop multiple different mechanisms to fight against drugs and survive, including the inhibition of apoptosis, drug expulsion, and increased proliferation. Recent studies have found unregulated cytokine expressions are highly involved in the drug resistance mechanism (Jones, V. S. et al. 2016).

Even though IFN-alpha and IL-2 do not provide very effective clinical outcomes, they are excellent candidates for combination therapy with other agents. In the past clinical trial, it was studied in the patients with hepatocellular carcinoma, which was not one of the diseases treated with IFN-alpha. In this trial, 106 patients with hepatocellular carcinoma received 5 million units of IFN-alpha on day 1,3,5 and each week of the treatment; meanwhile, they also received 5-fluorouracil (5-FU) 500mg on day 1-5 during the first two weeks of the 4-week cycle. The 5-FU is a standard medication used in hepatocellular carcinoma, so in the trial, people compared the combination with IFN-alpha with the standard therapy alone from the historical data. It turned out, about 20% of patients in the treatment group showed complete response and 36% of patients showed partial response. The efficacy was improved significantly compared to the standard therapy alone. The survival rate at 1-year and 2-year time points were 34% and 18%, while historically, with patients treated with standard therapy, the survival rate was 15% and 5%. Therefore, the survival rate largely improved with the combination of IFN-alpha, and the combination therapy was safe and more clinically effective (Obi, S. et al. 2006). From this example, the future of this class of medication should be

emphasized on the combination therapy with other agents due to its unique mechanism of action.

6 PREDICTED IMPROVEMENTS OF CYTOKINES

The biological basis and rationale of the use of cytokines are powerful, however, the clinical use of this technology faces a range of issues. There are some possible improvements in cytokine technology which researchers are going to do next. Firstly, improving pharmacokinetics and pharmacodynamics. Clinical pharmacology is the study of the interaction between the human body and drugs. Pharmacokinetics and pharmacodynamics are the two main branches of clinical pharmacology. Pharmacokinetic describes the absorption, distribution, metabolism, and excretion of drugs (ADME), while pharmacodynamic describes how biological processes in the body respond to or are affected by drugs (Otagiri, M., Imai, T., & Fukuhara, A. 1999). Pharmacokinetics and pharmacodynamics were vital in determining the safety and effectiveness of drugs. Secondly, improving local injection. Some cytokines can be produced in the laboratory and used to treat cancer. Some are used to help prevent or control the side effects of chemotherapy. They are injected under the skin, into muscles or veins. The two most common types are interleukins and interferons (Zhang, Z. & An, J. 2007). IFN-beta can be injected in areas of the body with a layer of fat between the skin and muscle, such as the thigh. However, interferon beta-1a can control the symptoms, but it cannot cure it. IL-2 and Interferon-alpha have been combined based on data from preclinical studies and have shown a synergistic effect. A review of available phase I and II trials with more than 1,400 patients indicated a response rate of approximately 20%, 3% to 5% of patients completely regressed. In order to prove that this combination improves the overall response rate, randomized trials were needed. The result of a phase III study displayed that, compared with patients who received either cytokine alone, patients treated with continuous infusion recombinant (r) IL-2 and subcutaneous IFN-alpha had a significant improved response rate 18.6% and 1-year event-free survival 20.9%. The clinical results are consistent with the improved response rate in patients receiving rIL-2 and IFN-alpha. Continued research on novel and new treatment methods remains a priority (Bukowski R. M. 2000).

Since the 1950s, a variety of cytokines have been used in the study of preclinical disease models, and with the development of recombinant protein technology in the 1980s, some of these cytokines have become successful biopharmaceutical products. However, due to cellular pleiotropy, the clinical translation of these innate immune signaling molecules is limited and they play primarily local roles in tissues. In view of the clinical potential and clinical trials in cancer immunotherapy, a range of molecular and formulation engineering strategies are being applied to reduce therapeutic toxicity while maintaining or enhancing therapeutic efficacy. Cytokine technology is promised to become more effective and widespread in the use of clinical treatment.

7 CONCLUSION

Cytokine therapy to activate the immune system of cancer patients is an important treatment method. The generation of a specific, effective cytokine-based immunotherapy requires a variety of cytokines and their receptors to combine with each other and give an optimum effect. Understanding the molecular signaling pathways of cytokine receptors is critical to the development of cytokine based cancer therapies. The most common cancers using cytokine-based therapy are kidney cancer, leukemia and lymphoma. These are the only three cancer types that use cytokine-targeted medications for treatment as monotherapy agents. This paper is introducing and comparing three subtypes of interferon in the treatment of kidney cancer, as well as the role of antitumor agent IFN-alpha in the treatment of leukemia and lymphoma. This paper derives from in-depth research on cytokine-based immunotherapy and its current barriers to indicate the future medication development focus using the study of hepatocellular carcinoma, and the combination therapy of IFN-alpha and the standard medication 5-FU on the treatment of hepatocellular carcinoma, which resulted a higher survival rate. The extensive pleiotropy and redundancy of cytokine signaling pathways suggest that cytokine therapy may use combination regimenes to amplify antitumor responses, inhibit regulatory pathways, and minimize toxicity. In general, cytokine based immunotherapy has shown its great potential, and cytokine therapy will have a broader prospect in the future.

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