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Research Progress of Interferon in the Treatment of Liver Cancer

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world and the fourth leading cause of cancer-related death. It is characterized by high incidence, poor prognosis, and high recurrence rates. Most patients are in an advanced stage when they seek treatment, and the therapeutic effect is not satisfactory. Interferon (IFNs) is a kind of cytokine with anti-virus, inhibition of cell proliferation, and induction of apoptosis, which has the advantages of improving cure rate, safe withdrawal of the drug, achieving sustained non-therapeutic immune response, reducing the incidence of liver cancer and avoiding the occurrence of drug resistance, delaying the progression of disease and improving the quality of life. Recent studies have found that IFNs can prevent the occurrence of viral hepatitis-related liver cancer and the recurrence and metastasis of liver cancer after surgery. Still, at the same time, there are also adverse reactions. This article reviews the mechanism of action, treatment, and adverse reactions of IFNs in liver cancer.

Keywords

Liver cancer, interferon, research progress

1. Introduction

According to the World Health Organization Annual Report on the Global Burden of Cancer 2020, the incidence of hepatocellular carcinoma (HCC) ranks sixth among malignant tumors and third among cancers in the world, while the incidence and fatality rate of HCC in China are also on the rise year by year [1]. Early HCC lacks specific clinical symptoms and hidden symptoms, and most patients lose the opportunity of surgical treatment when they are found to have developed to the middle and late stages. However, the current clinical interventional, immune, and targeted drug treatments are effective, but still cannot reach the ideal level, and have certain adverse reactions and side effects [2].

Interferon (IFN) is a kind of immune cytokine with a wide range of biological activities, which has a variety of biological functions, such as antiviral, anti-angiogenesis, immunomodulatory, anti-proliferation, and so on. According to secretory cells, gene sequence, and amino acid composition, IFNs can be divided into three categories: Class I includes IFN-αand IFN-β, class II is IFN-γ, and class III is IFN-λ.

2. Mechanism of IFNs in the treatment of liver cancer

2.1 Antiviral effect

Chronic hepatitis B virus (HBV) infection is associated with the development of serious liver diseases such as cirrhosis, hepatocellular carcinoma, and liver failure. The covalently closed circular DNA (cccDNA) of the hepatitis virus exists in the nucleus of the infected liver as an exome chromosome and serves as a template for viral mRNA

transcription. Junjun Cheng et al. [3] found that IFN- α can induce three cellular proteins, which can inhibit cccDNA transcription and cause the reduction of viral RNA. The study found that the cccDNA level of HBV was slightly decreased after NAs treatment. Because it does not directly target cccDNA [4], the cccDNA level of HBV was significantly reduced after treatment with PEG-IFN-alpha. IFN-αinduces the production of P48, which interacts with the original interferon-stimulated response at the enhancer promoter region of the HBV genome and inhibits HBV DNA replication. By binding to interferon receptors on the cell membrane, interferon induces the production of various antiviral proteins, such as protein kinases, which impede viral nucleic acid and protein synthesis. Adenosine deaminase (ADAR) is one of these proteins. It is widely found in various tissues and is involved in many physiological processes. Studies have shown that ADAR1 is involved in the occurrence and development of common tumors. IFN-α can promote the ubiquitination degradation of ADAR1, thereby weakening the inhibition of its anti-viral signal, and thus enhancing the antiviral effect of IFN-α [5].

2.2 Anti-angiogenic effect

The blood supply of liver cancer is very rich, and the angiogenesis process and the production of pro-angiogenic factors play a key role in the process of weight growth, invasion, and metastasis. The formation of neovascularization is conducive to the rapid growth, invasion, and metastasis of malignant tumors. Interferon can achieve anti-angiogenic effects by down-regulating vascular endothelial growth factor (VEGF) and inhibiting hepatocyte growth factor (HGF). In addition, IFN-γ can inhibit tumor metastasis by inhibiting the expression of matrix metallo proteinases (MMPs). MMPs can destroy the histological barrier of tumor cell invasion and promote the growth of tumor blood vessels. IFN-γ can inhibit the expression of MMPs and thus inhibit the tumor metastasis.

Basal membrane proteoglycans bind and supply growth factors, which are closely related to the growth and metastasis of tumor cells. IFN-γ can inhibit the tumor growth and metastasis by binding to heparin sulfate side chain on the basement membrane proteoglycans, and effectively block the gene expression of the basement membrane proteoglycans.

2.3 Immunomodulatory effects

IFN-γ plays an important role in tumor immunity. It is the only interferon family that can regulate the expression of MHC-IIantigen, and the expression of MHC-IImolecules determines the occurrence of immune response. By binding to receptors, interferon has regulatory effects on a variety of cytokines, including growth factors, protein kinases and tyrosine kinases, signaling processes, and induction of differentiation. IFN-γ can up-regulate the pathways related to MHC-Class I antigen processing and presentation, enhance the immunogenicity of tumor cells, induce autophagy, and inhibit cell proliferation [6]. PCNA is an important gene that marks cell proliferation; Cyclin D1 mainly promotes cell proliferation by accelerating the G1/S phase of the cell cycle. P21, a negative regulator of cell proliferation, can inhibit Cyclin E. Studies have shown that IFN-γ can significantly inhibit the growth and the proliferation of mouse Hepa1-6 liver cancer cell line, which is related to the decreased expression of PCNA and Cyclin D1 proteins and the increased expression of P21 proteins [7]. In addition, studies [8] have found that IFN-α can promote the expression of PD-1 in Tfh cells, indicating that the number of Tfh cells can be regulated by IFN-αregulating the expression of PD-1. IFN can promote the expression of chemokines in dendritic cells (DC), thereby recruiting NK cells, T cells and B cells to the infected area, and can induce the expression of IL15, which is very important for the maintenance of CD8+ memory cells and NK cells. IFN-Ican promote the activation of adaptive immune response by regulating cytokine expression in mucosal immunity [9].

2.4 Inhibit cell proliferation

Cell proliferation is an important process for maintaining human life, however, when the cell proliferation mechanism is dysfunctional, cells will proliferate uncontrollably and form tumors. Studies have shown that IFN- α can directly inhibit the proliferation of liver cancer cell line BEL-7402 in vivo and in vitro, and has a significant inhibitory effect on the invasion of BEL-7402 cells. Human interferon-induced transmembrane protein 3 (IFITM3), a member of the IFITM gene family, can be induced by type I and type II interferons and encodes interferon-induced transmembrane protein 3. It has been found that down-regulation of IFITM3 expression can reduce the proliferation ability of hepatocellular carcinoma cells, and inhibit the invasion and migration ability of hepatocellular carcinoma cells, suggesting that interferon indirectly affects IFITM3 to inhibit the proliferation of cancer cells.

2.5 Induction of apoptosis

Apoptosis plays a negative regulatory role on tumor. The occurrence and development of tumor are not only due to the increase in cell proliferation rate but also related to the decrease in cell apoptosis rate. Apoptosis has a certain significance in the evaluation of tumor prognosis. IFN-γ combined with all-trans retinoic acid (ATRA) has a synergistic effect on growth inhibition and apoptosis induction of hepatocellular carcinoma cells. Tnf-associated apoptosis-inducing ligand (TRAIL) is a novel apoptosis molecule that can induce apoptosis of a variety of tumor cells but has no killing effect on most normal cells. IFN-γ can enhance the degree of association of TRAIL to death receptors and further enhance the apoptosis-inducing effect of TRAIL by up-regulating the expression of TRAIL.

2.6 Regulation of cell cycle

The cell cycle is closely related to tumor. The cell cycle mainly includes the mechanism of cell cycle driving and regulation. When the regulation mechanism of the cell cycle is destroyed, the cell growth may be out of control, and it may be transformed into tumor cells. IFN combined with 5-fluorouracil (5-FU) can synergically inhibit the growth of liver cancer. IFN can reduce the activity of related kinases such as cell cycle-dependent kinase 2 by down-regulating the expression of cyclin D1, blocking tumor cells from the G1 phase to the S phase, and enhancing the cytotoxic effect of 5-FU. In addition, IFN can prevent the transformation of cells from the G0 to the S phase by inhibiting the expression of c-myc, thus playing an anti-tumor role.

3. Model of interferon therapy for liver cancer

3.1 Interferon monotherapy

Interferon monotherapy was mostly used for HBeag-negative patients with low viral load. Li M et al. [10] selected the initially treated HBeAg-negative patients for interferon therapy. The results showed that the HBsAg clearance rate was 3.7% at 48 weeks, and 6.2% at 72, 96, and 120 weeks, respectively. 11.1% and 14.8% of HBsag clearance. Prolonged treatment can lead to improved HBsAg clearance. Triplex sequence proteins (TRIMs) area family of proteins that play an important role in antiviral innate immunity, and members can effectively inhibit HBV. It has been found that TRIM19 [11] and TRIM38 [12] can inhibit HBV and can be induced by IFN-α. In a study followed for 11.5 years [13], higher rates of HBeAg serologic conversion and negative HBsAg conversion were observed in HBeAg-positive hepatitis B patients treated with interferon, while no significant difference in rates of HBsAg loss was observed between patients treated with short-term and long-term therapy. At the same time, by suspending the use of interferon, the function of the immune response can be restored in patients, creating conditions for patients to obtain clinical results by using interferon again. Some studies [14] found that HBsAg levels decreased slowly during the 58-71 weeks of IFN combined with tenofovir treatment. Therefore, the use of IFN was suspended and only tenofovir treatment was applied. After the 71 weeks of IFN combined with IFN again, serological conversion between HBeAg and HBsAg was observed at the 96th and 122nd weeks. This intermittent treatment regimen provides a new idea for reducing the adverse actions caused by long-term use of interferon.

3.2 Interferon combination therapy

Interferon combination regimens have been widely used in various tumors, such as the treatment of chronic myeloid leukemia with imatinib [15] and combined with lenalidomide for multiple myeloma [16]. Similarly, the combination regimen of interferon plays a vital role in the treatment of liver cancer. IFN combined with adefovir (ADV) therapy contributed more to the decrease of HBsAg and HBV DNA levels than ADV monotherapy [17]. In addition, IFN-α combined with T α1 has a synergistic effect on antiviral activity and has long-lasting efficacy [18]. The combination of entecavir early stage is more beneficial to the decline of HBsAg than the combination of entecavir at late stage [19]. A retrospective study [20] found that the negative conversion ratio of HBeAg in the IFN combined with Chinese medicine treatment group was significantly higher than that in the control group at 12, 18 and 24 months of follow-up, and the replication rate of HBV-DNA was significantly lower than that in the control group. Compared with NAs or Peg-IFN-α monotherapy, NAs combined with IFN therapy can improve HBsAg clearance and HBeAg negative conversion rate [21]. Hu et al. [22]found that for unresectable hepatocellular carcinoma, interferon combined with PD-1 therapy can significantly improve the tumor control rate.

3.3 Sequential combination therapy with interferon

In the current treatment model, sequential combination therapy mainly includes initial interferon combined with

nucleoside (acid); after interferon treatment for a period of time, the combination of nucleoside (acid) and so on. Jin [24] found that when entecavir was initially given for 10 weeks and then interferon sequential treatment for 28 weeks, the total effective rate was 97.14%, while the total effective rate was 82.86% when only interferon therapy was used, suggesting that the sequential treatment of Entecavir and interferon could improve the inhibition time of interferon on the virus. Results of a randomized controlled study on immune tolerance in children with chronic hepatitis B [25] showed that sequential antiviral therapy with interferon combined with lamivudine could significantly improve serum HBV DNA, HBeAg negative transfer rate, and HBsAg negative transfer rate in children.

3.4 Interferon postoperative adjuvant therapy

The recurrence of malignant tumors is still inevitable for patients with liver cancer after radical surgery such as resection and liver transplantation. The majority of patients with primary liver cancer are accompanied by basic diseases such as hepatitis and cirrhosis, and the immunity of the body is reduced, especially after liver cancer patients receive tumor resection, the immunity is increasingly decreased, or it may become one of the important factors for tumor recurrence. The peak time of HCC postoperative recurrence is 1~2 years after surgery, with intrahepatic recurrence being the most common. Studies have shown that postoperative interferon-assisted therapy can reduce the postoperative recurrence of hepatitis B and hepatitis C associated HCC, improve the prognosis of patients, and improve the quality of life of patients.

4. Adverse effects of interferon

4.1 Flu-like symptoms are the most common, with clinical manifestations

Similar to common colds, such as fever, headache, Myalgia, among which fever is the most common, which is due to interferon injection as a straight. The heat source induces the immune response to further produce some thermogenic cytokines, which feed back to the heat centers leading to fever.

4.2 Transient myelosuppression

Interferon has an inhibitory effect on the growth and proliferation of cells, which can be clinically manifested as a decrease in the levels of white blood cells, platelets, and reticulocytes. Therefore, when using interferon, we should adjust the program in time according to the changes in the patient's three lines.

4.3 Symptoms of Digestive tract

In the use of interferon often appear, such as common nausea, poor stomach, diarrhea, and other symptoms. Generally not treated, if necessary symptomatic treatment.

4.4 Neuropsychiatric symptoms

The main manifestations are depression, anxiety, and other symptoms. It is not recommended to use interferon clinically for patients with a history of mental illness and family history. If the patient has neuropsychiatric symptoms during treatment, timely measures should be taken and the drug should be stopped immediately.

4.5 Skin Reactions

Early manifestations of the skin are diffuse erythema on the trunk and limbs, urticaria, local skin itching, and can even induce psoriasis. Generally mild patients will not be treated, if necessary, you can consider stopping or reducing the drug, and prophylactic anti-allergy treatment.

4.6 Autoimmune diseases

Interferons can induce the production of autoantibodies, which can cause autoimmune diseases. Therefore, before the use of interferon, it is necessary to routinely check the patient's autoimmune antibodies, etc, review in time during the treatment, and pay attention to the adverse reactions of patients.

4.7 Changes in urinary system

Changes in kidney function can occur during treatment, including proteinuria, hematuria, and even increased

creatinine urea nitrogen, but most recover on their own when interferon is stopped. People with renal insufficiency should be given a high-quality low-protein, high-calcium, and low-phosphorus diet.

5. Conclusion

Hepatocellular carcinoma (HCC) is a malignant tumor of liver cells that usually begins insidiously and progresses rapidly. At diagnosis, most patients have locally advanced tumors or distant metastases, making HCC difficult to treat. With the improvement of modern medical treatment, the therapeutic effect of liver cancer has been continuously improved, and the quality of life of patients has improved. The fundamental improvement of the curative effect of liver cancer depends on the improvement of various research levels, such as further understanding of the occurrence, development, and mechanism of liver cancer, understanding the metastasis and recurrence mechanism of liver cancer after resection, identifying the specific antigen and gene of liver cancer as well as the signaling mechanism of its function and the signaling pathway. Clinically still adhere to the principle of early diagnosis and early treatment, according to the situation of patients, the current treatments are integrated and optimized, and the optimized treatment plan suitable for different individuals is obtained. Interferon, as a new antiviral drug, has been widely used in various tumors in recent years and has achieved remarkable clinical efficacy. However, with the wide application of interferon, its adverse reactions are gradually found, so how to play the best effect of interferon in the treatment of liver cancer and the best drug compatibility and other issues need to be further studied and explored.

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