

Summary of Tyrosine Kinase STI-571 in the Treatment of Chronic Myeloid Leukemia

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Abstract: Chronic Myeloid Leukemia (CML) is a hematological malignancy characterized by the presence of the Philadelphia chromosome, which results in the formation of the BCR-ABL fusion protein with constitutive tyrosine kinase activity. The discovery and development of targeted therapies, such as the tyrosine kinase inhibitor STI-571 (Imatinib), revolutionized the treatment of CML by specifically inhibiting the BCR-ABL kinase activity. This abstract provides a summary of the therapeutic efficacy and clinical impact of STI-571 in the management of CML. STI-571, a specific tyrosine kinase inhibitor, is a novel antitumor drug that has entered clinical trials and can effectively treat chronic myeloid leukemia caused by abnormal proliferation of hematopoietic stem cells. In this paper, the mechanism of action and regulation of cell cycle of this drug were summarized, and the problems of drug resistance were explored in depth and the development prospects of this drug were briefly introduced. The introduction of STI-571 has dramatically changed the management of CML, leading to a paradigm shift from conventional chemotherapy and allogeneic stem cell transplantation as the primary treatment options. The drug has shown superior efficacy compared to interferon-alpha therapy, the standard treatment before its introduction. STI-571 is generally well-tolerated, with fewer severe adverse effects, making it an attractive option for long-term therapy. Resistance to STI-571 has been observed in a subset of patients, primarily due to the emergence of BCR-ABL kinase domain mutations. However, the development of second-generation tyrosine kinase inhibitors, such as dasatinib and nilotinib, has provided alternative treatment options for patients who fail to respond to or develop resistance to STI-571.

Keywords: STI-571; Chronic Myeloid Leukemia; The Cell Cycle Gene and Protein.

1. Introduction of the Chronic Myeloid Leukemia and Current Situation

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder caused by a misalignment of chromosome 22 resulting in the replacement of one of the genes c-Abl with the Bcr-Abl gene. The Bcr-Abl gene expresses the Bcr-Abl protein, which has abnormal tyrosine kinase activity and induces myeloid cell proliferation. The total incidence of leukemia in our country is about 2.76 people per 100 000 person-time, among them, with myeloid leukemia is more common, the incidence of disease is about 0.36 per 100 000 person-time.[1]

2. The Difficulties of Treatment of the Chronic Myeloid Leukemia

The treatment of chronic myeloid leukemia has been a difficult problem for medical research in past few years because this disease has many mechanisms that are not easy to spot and its cause is very complex. For example, the X-ray can lead to this disease because it can decrease the immunity of the body and make the DNA mutate or recombine. Also, chemical factor can cause the disease, such as the close touch of the benzene for a long time. Chronic myeloid leukemia often has a very long course, because the early onset symptoms are not very obvious, the onset of the disease is relatively slow, so it may be discovered late, resulting in a more serious condition caused by delayed detection. Plus, and more difficult to treat, most common to cure leukemia inhibitory drugs for Bcr-Abl gene targeting is not strong, especially in patients with stage accelerated and blast, many patients with leukemia cells may not particularly sensitive to

chemotherapy drugs, so the efficacy for patients is not very enough, which leads to poor treatment effect, Repeated illness, chronic problems. In addition, some drugs have relatively large side effects and do great physical harm to patients. [1] Therefore, the study of new targeted drugs that precisely target BCR-ABL gene and inhibit its tyrosine kinase activity may be an effective method for the treatment of chronic myeloid leukemia.

3. The Introduction of Tyrosine Kinases

Tyrosine kinases are important proteins that control cell growth and differentiation. They are members of the oncoprotein and proto-oncoprotein families that play important roles in normal and abnormal cell proliferation and play key roles in normal cell division and abnormal cell proliferation. Tyrosine kinases are the products of many proto-oncogenes. When tyrosine kinase activation, is to start the DNA synthesis and cell proliferation of cells key signal, a lot of retrovirus cancer gene encoding protein and a variety of growth factors transmembrane receptors have tyrosine kinase activity, tyrosine kinase is not only involved in hormone and growth factors and extra-cellular information transmission, also related to cell proliferation and malignant transformation. Therefore, tyrosine kinases play an important role in the genesis and development of tumors. Effective inhibition of tyrosine kinase activity may be an effective treatment for chronic myeloid leukemia. [1,2]

4. The Introduction of STI-571 and its Functions

4.1. The Introduction of New Drug for Treating CML, STI-571

A recent new drug, the tyrosine kinase inhibitor STI-571, may be a new drug for the treatment of chronic myeloid leukemia because the tyrosine kinase inhibitor effectively targets the Bcr-Alc gene expressing tyrosine kinase. Sti-571 specifically competes for ATP sites, which specifically inhibits tyrosine kinase activity, thereby affecting the proliferation of cancer cells. Sti-571 can effectively inhibit the proliferation of 32D cells infected with Bcr-Alc gene and reduce the activity of abnormal tyrosine kinase by 92% to 98%, thus effectively inducing abnormal cell apoptosis and achieving the effect of effective treatment of leukemia.[2,3]

4.2. The Mode of Action of STI-571

It was found that the tyrosine kinase inhibitor STI-571 could also influence the cell cycle to influence abnormal tyrosine kinase activity. The proteins affected are P38, P27, cyclinD1 and so on. Recently, experiments have studied the effects of STI-571 on three proteins. P27 protein can prevent or slow down cell division. In the early stage of cell division, the expression of P27 protein increases, which stops cell division in the middle stage and inhibits cell proliferation. When the P27 protein is highly expressed, DNA synthesis is strongly blocked. When the P27 protein was reduced by 80%, DNA synthesis increased. P27 also regulates the cell cycle by regulating the activity of cyclinE, so p27 plays an important role in cell division. P38 protein is a mitogen-activated protein kinase that is involved in the regulation of apoptosis, cell cycle arrest and cytokine production, and plays an important role in cell division. [3] CyclinD2 is an important gene in cell cycle genes and an important information transfer molecule. The protein cyclinD2 is a type of cyclin. It plays an important monitoring role in the pro-phase of cell division. CyclinD2 gene expression is abnormally elevated in patients with chronic myeloid leukemia. CyclinE protein is a kind of cell cycle protein, which accumulates during the inter-phase

of cell division and regulates cell division. After the inter-phase of division, it is degraded by specific protease. [3] However, if the degradation pathway of this protein is defective, it will lead to the acceleration of the cell into the division phase, which will lead to the genetic instability of cell division and easily lead to cell canceration. Therefore, to effectively explore how STI-571 affects the concentration of key genes in important cell cycle genes is an important way to prove whether STI-571 is effective in the treatment of chronic myeloid leukemia.

In chronic myeloid leukemia, reduced p27 protein expression leads to Bcr-ALC gene expression, resulting in abnormal tyrosine kinase activity. The expression level of cyclinD2 is low in normal subjects, but high in patients with chronic myeloid leukemia. Studies have found that cyclinD2 and cyclinE are extremely effective on Bcr-ALC protein proliferation, but inhibition of 50%cyclinD2 protein function or expression can effectively inhibit Bcr-ALC protein expression. In addition, the P38 protein (MARK) is also a cell transmitter in the cell cycle. In patients with chronic myeloid leukemia, p38 protein expression levels are also high, leading to abnormal cell proliferation and abnormal protein expression. Therefore, the effects of STI-571 on the above proteins were investigated.[3]

4.3. The Experiment Data

After the infected leukemia cells were treated with sti-571 for 12h, the expressions of p27, p38, cyclinD2 and cyclinE genes were as Table 1 follows:

Table 1. The change of genes in 12h

	P27 gene	P38 gene	cyclinD2 gene	cyclinE gene
Experimental group	0.65	0.16	0.21	0.15
Control group	0.35	0.66	0.89	0.64

After the infected leukemia cells were treated with sti-571 for 12h, the expressions of p27, p38, cyclinD2 and cyclinE proteins were Table 2 as follows:

Table 2. The change of proteins in 12h

	P27 proteins	P38 proteins	cyclinD2 proteins	cyclinE proteins
Experimental group	0.98	0.17	0.19	0.25
Control group	0.36	0.68	0.36	0.98

After the infected leukemia cells were treated with sti-571 for 12h and 72h, the distributions of cell cycle were as Table 3 follows:

Table 3. The number of leukemia cells in different cell division period in 12h and 72h

	G0/G1 period	S period	G2/M period
Experimental group 12h	76.8	23.2	8.3
Experimental group 72h	92.4	11.5	7.8
Control group	32.4	62.8	15.8

According to the above data, the cell cycle of the leukemia cells treated with sti-571 was arrested at the inter-division stage, showing an obvious change trend at 12h, and most cells were arrested at the pro-phase of cell division after 72h. The

activity of proteins (cyclinD2 and cyclinE) that promote tyrosine kinase activity and cell division and proliferation were effectively inhibited, including the cell signaling pathway (P38) of chronic myeloid leukemia. In contrast, the

p27 protein, which monitors and inhibits abnormal cell proliferation, increased. [2,3]

4.4. The Conclusion

According to the above data, the important proteins regulating the cell cycle in the leukemia cells treated with STI-571 were significantly changed. The expression level of P27 protein increased significantly, which was positively correlated. The expression of cyclinD2, cyclinE and P38 decreased significantly, showing negative correlation. The number of cells in the inter-phase of cell division increased, and the number of cells in the inter-phase decreased. These results indicate that STI-571 can effectively prevent cells from entering the cell division stage by inhibiting and regulating several important targets in the cell conduction pathway, and the cell division stage is stopped in the inter-division stage, and finally inhibits the proliferation of chronic myeloid leukemia cells.[3]

5. The Clinical Manifestation

So far, STI-571 has been clinically used. Druker BJ of Duke University enrolled 80 patients in a clinical study of chronic myeloid leukemia treated with conventional therapies. The results showed that STI-571 was well tolerated and had obvious therapeutic effect on chronic myeloid leukemia. After four weeks of treatment, more than 90 percent of the patients returned to normal levels of white blood cells. After 4 months of treatment, 50% of patients had a cytological genetic response and 13% had a cytogenetic complete response. In the patients studied, cytogenetic remission was first observed after 2 months of treatment and was most recently observed after 10 months of treatment, with an average duration of 4 to 5 months.

In addition, clinical studies have found that side effects of STI-571 include nausea, edema, muscle soreness and diarrhea, but these are mostly mild and tolerable for patients. In a small number of patients, more serious side effects, such as anemia and thrombocytopenia, can be alleviated by reducing dosage or stopping medication for a period of time.[4]

6. The Drug Resistance of STI-571 and Related, Effective and Possible Solutions

6.1. The Generation of the Drug-Resistance of STI-571

From the above data, it can be seen that STI-571 is very effective in the treatment of chronic myeloid leukemia. But with the widespread use of the drug in recent years, resistance has developed. There may be several reasons for the generation of drug resistance: first, bCR-ALC gene

amplification, second, bCR-ALC gene transcription changes, third, BCR-ALC gene translation changes, fourth, BCR-ALC gene mutation, thus reducing the combination of STI-571 and producing drug resistance.

6.2. The Solutions of the Drug-Resistance of STI-571

So, how to overcome the many problems caused by drug resistance has become a new research direction. Recent studies have shown that when patients develop resistance and stop taking STI-571 for a period of time, cell resistance decreases and sensitivity increases, so intermittent administration may help prevent resistance. Other ways to reduce resistance can be taken in combination with other drugs, such as erythromycin, which inhibits p-glycoprotein. [4] Other drugs include arsenic trioxide, which in combination with STI-571 was found to inhibit bCR-ALC gene expression. Sti-571 can also be used in conjunction with other protein kinase inhibitors to effectively overcome drug resistance. For example, extracellular signal-regulated kinase inhibitors, used in combination with STI-571, can effectively induce apoptosis in leukemia cells. The cyclin-dependent kinase Flavopiridol can also cooperate with STI-571 to significantly increase mitochondrial damage and apoptosis of BCR-AIC protein by STI-571, which may be an effective approach.[4]

7. The Future of Developing STI-571

Since the mechanism of drug resistance is extremely complex, STI-571 combined with multiple targeted inhibitors may be a better treatment for chronic myeloid leukemia. Though there are still some problems needed to be solved, STI-571 is a good drug to treat the chronic myeloid leukemia. I believe that with further research and exploration of the mechanism of STI-571 resistance, chronic myeloid leukemia can be effectively treated.

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