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The Efficacy and Improvement Methods of Multi-Kinase Inhibitors in the Treatment of Liver Cancer

Xinyue Wang

Rosedale Global High School
Taiyuan, China
cherry950820@gmail.com

Abstract:

Liver cancer is a malignant tumor with an extremely high fatality rate worldwide, and traditional treatment methods have significant limitations. This thesis systematically explores the application of multi-kinase inhibitors in the treatment of liver cancer and deeply analyzes its dual mechanism of action: inhibiting tumor angiogenesis by blocking signaling pathways such as VEGF and PDGF, and simultaneously interfering with pathways such as MAPK to curb the proliferation of tumor cells. Based on key clinical research data such as SHARP and REFLECT, the survival benefits of monotherapy with drugs such as sorafenib and lenvatinib were elaborated in detail. The median survival period increased to 10.7-13.6 months, but the problems of drug resistance and adverse reactions were prominent. Combined immunotherapy and local treatment show the potential for synergistic enhancement. Studies have confirmed that screening for advantageous populations such as FGFR mutations through genetic testing can significantly improve the accuracy of treatment. This article aims to provide a comprehensive theoretical basis and innovative strategies for optimizing targeted therapy regimens for liver cancer and promoting clinical practice.

Keywords:-Multi-kinase inhibitors, Liver cancer, Drug resistance, Clinical application, Targeted therapy

I. Introduction

Liver cancer is one of the main causes of tumor-related deaths worldwide. According to the global cancer statistics of 2024, there are over 850,000 new cases of liver cancer and nearly 768,000 deaths. In China, due to the large number of hepatitis B and C infections, the incidence and mortality rates of liver cancer have remained consistently high. Epidemiological investigations show that about 80% of liver cancer patients in China are already in the middle or advanced stage at the initial diagnosis, missing the best opportunity for radical surgery. The 5-year survival rate is only 5% to 15%. Traditional chemother-

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apy methods have limited therapeutic effects due to the high heterogeneity of liver cancer cells and the obvious toxic and side effects of chemotherapy drugs. Although liver transplantation is a potential radical cure, it is limited by the shortage of donors and strict indications. Local ablation therapy is restricted by factors such as the size and location of the tumor burden, and its application scope is relatively narrow. The emergence of targeted therapy has brought new opportunities for the diagnosis and treatment of liver cancer. Multi-kinase inhibitors can act on multiple tumor-related kinase targets simultaneously. By inhibiting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), etc., they effectively interfere with tumor angiogenesis and cell proliferation signaling pathways, becoming the cornerstone of first-line treatment for advanced liver cancer. Since sorafenib was approved for marketing in 2007, it has ushered in a new era of targeted therapy for liver cancer. Subsequently, drugs such as lenvatinib and regorafenib have been successively introduced, continuously refreshing the survival data of liver cancer patients [1]. However, in clinical practice, there are still urgent problems to be solved, such as single-drug resistance, adverse reactions, and significant differences in therapeutic effects among different patients. Therefore, in-depth research on the mechanism of action of multi-kinase inhibitors in the treatment of liver cancer and optimization of treatment plans are of great significance for improving the quality of life of patients with liver cancer. This article will systematically review the mechanism of action, clinical efficacy and bottlenecks of multi-kinase inhibitors, and explore combined treatment and precision medication strategies, providing theoretical support for promoting the practice of precision medicine in liver cancer.

II. Principle

A. Mechanism of Action of Multi-kinase inhibitors

Multi-kinase inhibitors act on various tyrosine kinase receptors such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). Blocking the VEGFR signal can inhibit tumor neovascularization and cut off the nutrient supply to the tumor. Inhibiting the PDGFR pathway can reduce abnormal remodeling of tumor blood vessels and lower tumor blood supply, just like “cutting off the nutrient delivery pipeline of the tumor”. Meanwhile, some multi-kinase inhibitors act on RAF kinase, interfere with the MAPK pathway, block the proliferation signals of tumor cells, and can also regulate the metabolism and proliferation of tumor cells by inhibiting fibroblast growth factor receptor (FGFR), thereby “inhibiting tumor growth at the source”.

B. Selectivity of Drug Action Targets

Different multi-kinase inhibitors have different pharmacokinetic and therapeutic characteristics due to different target combinations. The half-life of sorafenib is approximately 25 to 48 hours, and it takes a certain amount of time to reach a stable blood drug concentration after administration. Lenvatinib reaches its peak within 1 to 4 hours and can take effect rapidly. Regorafenib requires continuous administration to maintain the blood drug concentration. When making clinical choices, the liver function of patients (such as Child-Pugh classification), comorbidities (such as a history of hypertension), and tumor molecular characteristics (such as FGFR mutations and high expression of VEGF) should be comprehensively considered to precisely match drugs and achieve the maximization of therapeutic effect and the minimization of toxicity [2].

C. Interaction with the Tumor Microenvironment

It can regulate the tumor microenvironment, influence the infiltration of immune cells and the remodeling of extracellular matrix, change the “soil” for tumor growth, enhance the body’s anti-tumor immune response, and exert a synergistic anti-tumor effect.

III. Therapeutic efficacy of multi-kinase inhibitors

A. Principle

As mentioned earlier, it functions by inhibiting tumor angiogenesis, cell proliferation-related kinases, and regulating the tumor microenvironment [3]. Represented by sorafenib and lenvatinib, sorafenib is the first multi-kinase inhibitor approved for systemic treatment of liver cancer, and lenvatinib has demonstrated advantages in subsequent studies. It is widely used in the first-line systemic treatment of unresectable liver cancer. With the advancement of clinical research, it is also being explored and applied in postoperative adjuvant therapy and combined immunotherapy for liver cancer, providing treatment options for patients with liver cancer at different stages. The advantages are that it can prolong the patient’s survival, control tumor progression and improve the quality of life. The drawback is that it is prone to drug resistance, with common adverse reactions such as hand-foot skin reactions and hypertension, and some patients have a poor response to the initial treatment.

B. Effect

1) Prolong the survival period

In the SHARP study, sorafenib enabled the median survival period of patients with advanced liver cancer to reach 10.7 months, which was higher than 7.9 months in the placebo group, establishing its cornerstone position in the systematic treatment of liver cancer. Studies in the Asia-Pacific region have also confirmed its effect of prolonging survival. In the REFLECT study, lenvatinib had a median overall survival that was not inferior to sorafenib (13.6 months and 12.3 months, respectively; the original data of 7.4 months might be incorrect; according to the actual study, it should be approximately 12.3 months), and a better progression-free survival (7.4 months vs 3.7 months). It shows good tumor control ability and brings survival benefits to patients. In clinical practice, for patients with advanced liver cancer who are inoperable, after using multi-kinase inhibitors, the survival period of some patients was significantly prolonged compared with traditional supportive treatment [4]. Follow-up found that the survival curve of patients with standardized medication shifted to the right, verifying the effect of drugs in prolonging survival.

2) Effectively control tumors

Imaging assessment shows that multi-kinase inhibitors have a significant inhibitory effect on tumor growth. After 12 weeks of lenvatinib treatment, the objective response rate reached 25% and the disease control rate was 75%. After 16 weeks of sorafenib treatment, the objective response rate was approximately 10%, and the disease control rate was approximately 50% [5]. Both could inhibit the tumor to a certain extent, manifested as the shrinkage and stability of the tumor lesion, and tumor angiography showed a reduction in tumor blood supply. After treatment, the levels of tumor markers such as alpha-fetoprotein (AFP) in patients decreased. For instance, after sorafenib treatment, the AFP level in some patients dropped from hundreds or even thousands to just a few dozen, indicating that tumor activity was inhibited and indirectly demonstrating the control effect on the tumor.

3) Improve the quality of life of patients

The adverse reactions of multi-kinase inhibitors are relatively mild and can maintain the quality of life of patients. After 3 months of treatment, patients showed significant improvement in terms of pain, physical strength, appetite, etc. For example, for patients using lenvatinib, the NRS score for pain decreased from 5-6 points to 2-3 points, and the ECOG score for physical strength improved from 2 points (limited physical strength, able to walk but requiring bed rest for more than 50% of the time) to 1 point (symptomatic, But it is almost completely free to move around.)

Measured by the score of the EORTC QLQ-C30 scale, after treatment, patients significantly improved in dimensions such as physical function, role function, and emotional function. The score in the functional domain increased, the score in the symptom domain decreased, and the overall quality of life improved [6].

C. Problem Discussion

After comparing sorafenib with lenvatinib, it was found that lenvatinib has advantages in progression-free survival and objective response rate [7]. However, sorafenib has been used in clinical practice for a longer time, and doctors have more experience in medication and more mature management of adverse reactions. Moreover, the drug resistance mechanisms of the two are different. Sorafenib resistance is related to secondary mutations of RAF kinase, etc. Lenvatinib resistance may involve bypass activation, and targeted exploration of subsequent treatment is needed.

However, there are still bottlenecks in monotherapy with multi-kinase inhibitors. For example, some patients have primary drug resistance, and the tumor progresses in the early stage of treatment. There is a lack of a unified and effective rescue plan after secondary drug resistance. Although adverse reactions can be managed, they still affect the medication compliance of some patients. It is necessary to explore dose adjustment and combination medication strategies to balance efficacy and safety [8].

The combination of multi-kinase inhibitors and immunotherapy is a research hotspot [9]. For example, lenvatinib combined with PD-1 inhibitors can further improve the tumor control rate and prolong survival through the synergistic effect of anti-angiogenesis and immune activation. However, it also faces the risk of superimposed adverse reactions, and it is necessary to optimize the combination regimen and explore biomarker screening for advantageous populations [10,11].

IV. Therapeutic efficacy of multi-kinase inhibitors

A. Synergistic Effect of combined therapy

1) Combined with immunotherapy

Combined immunotherapy, such as in the KEYKeynote 524 study, achieved an objective response rate of 56% for pembrolizumab combined with lenvatinib, a disease control rate of 91%, and a median progression-free survival of 9.3 months [12]. Combined therapy activates the immune response of the body and works in synergy with multi-kinase inhibitors to fight tumors. For patients with advanced liver cancer, the median overall survival of multi-kinase

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inhibitors combined with PD-1 / PD-L1 monoclonal antibodies is prolonged to 28 months, which is longer than the 18 months of lenvatinib alone, achieving the synergy of local and systemic treatments and improving the therapeutic effect.

2) In combination with local treatment

Multi-kinase inhibitors combined with local treatments such as transcatheter arterial chemoembolization (TACE) and radiofrequency ablation have also shown advantages. For liver cancer patients who can undergo local treatment, local treatments such as TACE should be implemented first, followed by the combination of multi-kinase inhibitors. This can enhance the tumor-killing effect, delay tumor recurrence, and prolong the survival period of patients. Different combination regimens have been continuously optimized in clinical exploration.

B. Precision Medicine and Patient Stratification

The dominant population was screened through genetic testing [13]. For patients with BRAF V600E mutation, the objective response rate of multi-kinase inhibitors combined with targeted drugs reached 40%. Precise genetic testing guides the dosage of multi-kinase inhibitors, which can reduce adverse reactions, improve compliance and ensure treatment [14]. Meanwhile, based on a comprehensive assessment of the patient's liver function, physical condition, etc., an individualized medication plan is formulated to achieve precise treatment and improve the therapeutic effect [15].

V. Examples

A. Synergistic Enhancement Mechanism of Combination Therapy: From Theory to Clinical Practice Sequential treatment: The dynamic balance between immune response and vascular normalization

The sequential treatment strategy of the Harvard University team has revealed the dynamic interaction between the immune system and the tumor microenvironment. PD-1 inhibitors (such as nivolumab) activate the initial immune response by relieving the state of T cell exhaustion, but they are limited by immunosuppressive TME when used alone. Subsequently, sorafenib (a multi-target kinase inhibitor) triggers the normalization of tumor blood vessels by inhibiting pathways such as VEGFR and PDGFR [16]

Promote vascular structure remodeling: Reduce abnormal vascular leakage, lower interstitial pressure, and promote T cell infiltration (CD8+ T cells increase by three times); Promote the optimization of the immune microenvironment: Increase the coverage of pericytes, reduce the recruitment of immunosuppressive cells (such as Tregs and MDSCs), and enhance the efficiency of antigen presentation.

Clinical verification: In mouse models, the ORR of sequential therapy reached 12% (2%-3% vs. sorafenib monotherapy), and the median OS was prolonged to 12.1 months [17]. This strategy provides a new idea for patients resistant to sorafenib, but the impact of the heterogeneity of human TME on the therapeutic effect needs to be further verified [18].

B. Anti-angiogenesis + immune checkpoint inhibitors: Breakthrough Insights from the IMbrave150 study

Atezolizumab (PD-L1 inhibitor) combined with bevacizumab (VEGF monoclonal antibody) shows significant advantages in first-line treatment:Survival benefit: Median OS 19.2 months (vs sorafenib 15.6 months), median PFS 6.8 months (vs 4.3 months). Improvement in response rate: ORR 27% (vs 11.9%), and the CR rate was as high as 6% [19].

The synergistic mechanism of bevacizumab enhances the effect of immunotherapy through the following pathways. Firstly, normalize the blood vessels, reduce VEGF-mediated vascular leakage, and lower the infiltration of immunosuppressive cells (such as Tregs and MDSCs); Secondly, immunogenic cell death (ICD), anti-angiogenic drugs induce tumor cells to release damage-related molecular patterns (DAMPs), and activate dendritic cells (DCs). Improved vascular permeability makes it easier for effector T cells to penetrate the tumor matrix [20].

Although the combination therapy significantly improved the therapeutic effect, the incidence of grade 3-4 adverse reactions was as high as 61% (56% vs. sorafenib), suggesting the need to optimize the dosage or explore new anti-angiogenic drugs (such as small molecule inhibitors) to reduce toxicity [21,22].

VI. Conclusions

Multi-kinase inhibitors reshape the pattern of targeted therapy for liver cancer. Drugs such as sorafenib and lenvatinib prolong the survival period of patients, but single-drug resistance and adverse reactions still limit clinical benefits. Combined therapy (in synergy with immunization and local treatment) shows potential for enhancing efficacy, and precise medication (screening the population based on genetic characteristics and clinical phenotypes) is the core of the optimization plan. In the future, it is necessary to deepen mechanism research (such as the interaction between the tumor microenvironment and targeted drugs), expand real-world data (differences in therapeutic effects among different populations), promote the upgrade of multi-kinase inhibitors from "broad-spectrum target-

ing" to "precise customization", provide more efficient and safer treatment options for liver cancer patients, help break through the bottleneck of liver cancer treatment, benefit more patients, and improve their quality of life and survival period.

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