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Research Progress in Molecular Typing and Targeted Therapy of Liver Cancer

Zhou Lin[1,a], Zhou Jun[2,b,*]

[1]*Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
[2]*Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China*
[a]*3465451874@qq.com,* [b]*13629106789@163.com*
[*]*Corresponding author*

Abstract: *Primary liver cancer is currently the fourth most common malignant tumor in China and the second leading cause of tumor mortality in Central Europe, posing a serious threat to the lives and health of the Chinese people. At present, the treatment plan for liver cancer is mainly surgical treatment, but the prognosis of many patients is unsatisfactory. Many patients even lose the opportunity for surgery when diagnosed. At a time when the treatment of liver cancer was stagnant, the emergence of molecular targeted chemotherapy drugs brought new hope to liver cancer patients. For example, the first to appear sorafenib brought revolutionary progress to the treatment of advanced liver cancer. However, due to limited understanding of the molecular typing of liver cancer, it was impossible to screen molecular targeted chemotherapy drugs for those patients, resulting in significant differences in patient responses to targeted therapy. Therefore, establishing a molecular typing scheme for liver cancer to guide clinical targeted therapy is particularly important. This review will briefly discuss the latest progress in molecular typing and targeted therapy for liver cancer.*

Keywords: *Liver cancer; Molecular typing; targeted therapy*

1. Introduction

Primary liver cancer is currently the fourth most common malignant tumor and the second leading cause of tumor death in China, Serious threat to the life and health of the Chinese people [1-3], as shown in Figure 1. Primary liver cancer mainly includes three different pathological types: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and mixed hepatocellular carcinoma cholangiocarcinoma (cHCC CCA), of which hepatocellular carcinoma accounts for the heaviest proportion, see Figure 2. According to statistics from the China Cancer Registration Annual Report, the overall 5-year survival rate of liver cancer in China from 2003 to 2015 was only 12 5% [4]. Epidemiological studies have confirmed that the main risk factor for liver cancer is hepatitis B virus (HBV) infection [5]. Secondly, hepatitis C virus (HCV), alcohol consumption, aflatoxin, metabolic factors, such as obesity and diabetes, may also be risk factors for liver cancer [6].

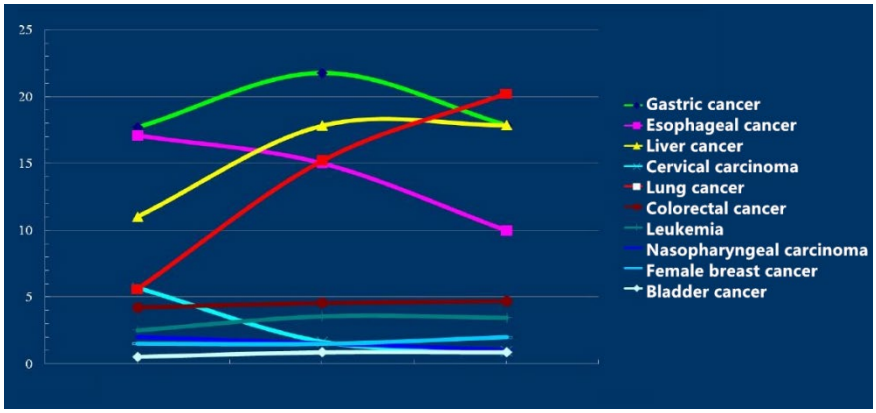

Figure 1: Ranking of causes of death in malignant tumors in China

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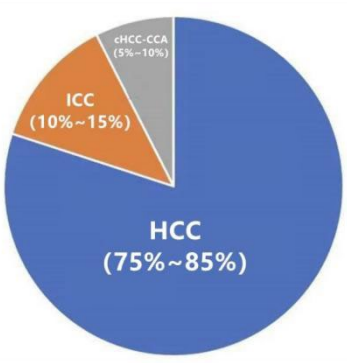

Figure 2: The proportion of different pathological types of primary liver cancer

For early liver cancer, surgical treatment can be chosen, as well as non-surgical treatment methods such as local ablation, radiation therapy, percutaneous hepatic artery chemoembolization, and systemic therapy. However, most liver cancer cases are insidious and progressing rapidly, making it difficult to detect and diagnose, resulting in most patients reaching local advanced stage or having distant metastasis at the time of diagnosis, and losing the opportunity for surgical surgery. For end-stage liver cancer patients, liver transplantation is one of the most effective methods recognized worldwide for treating end-stage liver disease. However, due to the difficulty of surgical techniques, high surgical costs, and many postoperative complications, liver transplantation has not been widely used.

Due to the complex pathological types of liver cancer, its pathogenesis, histopathology, biological behavior, treatment methods, and prognosis are also different, so its treatment effect is not satisfactory. Chemotherapy, radiotherapy, and some traditional Chinese medicine treatment methods are often used as adjunctive treatments before and after malignant tumor surgery, which have a certain therapeutic effect on the disease. However, it is not used for all patients, and chemotherapy and radiotherapy have gastrointestinal reactions Toxic side effects such as bone marrow suppression and local mucosal damage make it difficult for some patients with poor physical fitness to tolerate the harm caused. In recent years, targeted treatment methods have emerged, which have less toxic side effects such as nausea, vomiting, hair loss, and liver dysfunction compared to radiotherapy and chemotherapy. Patients have better tolerance and can significantly improve their quality of life. By studying the molecular typing of liver cancer, guiding targeted therapy has brought new opportunities for liver cancer treatment. Starting from molecular typing, exploring biomarkers for molecular targeted therapy can screen suitable populations for drugs and accurately predict their efficacy and prognosis. To achieve the expected results in the treatment of liver cancer, in 2007, the first tyrosine kinase inhibitor for liver cancer targeted therapy, Sorafenib toluenesulfonate, was approved, ushering in a new era of targeted therapy for liver cancer. Therefore, this article summarizes some molecular typing and targeted therapy drugs related to liver cancer, in order to provide new ideas for the development of targeted therapy for liver cancer.

2. Molecular typing of liver cancer

The occurrence of liver cancer is a complex process that is multifactorial, multi-step, and regulated by multiple mechanisms, with high heterogeneity. At present, the development of clinical treatment plans based on the general classification and histopathological classification of liver cancer is an important basis for predicting and judging the prognosis and prognosis of patients. However, its effectiveness is not significant. With the rapid development of genomics, we have realized that even liver cancer patients in the same clinical stage have significant differences in the molecular level characterization of tumor cells. For example, classifying patients based on molecular typing and then administering different drugs for treatment can result in significantly different clinical efficacy and prognosis [7-9]. For example, in breast cancer, gastric cancer and other diseases, the patients are classified according to their genetic characteristics, and then the patients who are sensitive to chemotherapy are screened out. After their surgery, adjuvant chemotherapy will have a therapeutic effect much better than those who are not sensitive to chemotherapy. Therefore, this method of screening in advance according to genetic characteristics will not only increase the therapeutic effect of patients who are sensitive to chemotherapy. It can also protect people who are not sensitive to chemotherapy from some of the toxic side effects brought about by chemotherapy, not only reducing their physical pain but also reducing their economic burden, and even allowing them to choose other

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effective treatments more quickly.

Liver cancer has a high degree of malignancy, low 5-year survival rate, and poor prognosis. The main reason is that liver cancer is prone to invading the portal vein and leading to intrahepatic dissemination, resulting in a high rate of intrahepatic metastasis and postoperative recurrence of liver cancer. However, some liver cancer patients with the same pathological diagnosis and clinical treatment can achieve long-term (tumor free) survival, which is sufficient to indicate the existence of different cell and molecular subtypes in liver cancer. Therefore, molecular typing is particularly important in the treatment of liver cancer. Research on molecular typing of liver cancer can not only serve as a biomarker for diagnosis and prediction of therapeutic effects, but also help us better study and explore the pathogenesis of different molecular types of liver cancer patients. Although there are differences in the results of integrated analysis based on genomics, transcriptomics, and epigenomics in different literature, high-frequency genes and major related pathways are basically consistent, and two main molecular subtypes of hepatocellular carcinoma based on molecular typing have been proposed: proliferative subtypes and non-proliferative subtypes [5].

3. Targeted therapy for liver cancer

With the development of society and technology, people's attitudes towards cancer treatment are undergoing a revolutionary change, shifting from empirical science to evidence-based medicine, and from cell attack mode to targeted treatment mode. Among them, the application of targeted technology to accurately deliver drugs to tumor areas through targeted therapy and the use of tumor specific signaling or metabolic pathways to control targeted therapy are hotspots in cancer research. Targeted therapy refers to a treatment approach at the cellular and molecular level that targets a well-defined carcinogenic site (which can be a protein molecule within a tumor cell or a gene fragment). Design corresponding therapeutic drugs for their carcinogenic sites. When the drugs enter the body, they will specifically select the carcinogenic site to combine and exert therapeutic effects, causing tumor cells to specifically die without affecting normal tissue cells around the tumor. Therefore, molecular targeted therapy is also known as "biological missiles".

According to the different targeting sites, tumor targeted therapy can be divided into two categories: tumor cell targeted therapy and tumor vascular targeted therapy. According to Hallmarks of Cancer: The Next Generation, strategies for targeted treatment of tumors are shown in Figure 3. Tumor cell targeted therapy refers to the use of specific antigens or receptors on the surface of tumor cells as targets, while tumor vascular targeted therapy uses specific antigens or receptors on the surface of newly formed capillary endothelial cells in the tumor area to act. Although the targeting properties of monoclonal antibodies targeting tumor cells have to some extent increased the concentration in local tumor tissue, these macromolecular substances still need to pass through the vascular endothelial cell barrier in order to reach the tumor cell target area, which is relatively slow. So vascular targeted drugs have great advantages, as they can quickly accumulate at high concentrations at the target site after administration. Targeted therapy for liver cancer mainly falls into two categories: simple angiogenesis inhibitors and multi kinase inhibitors.

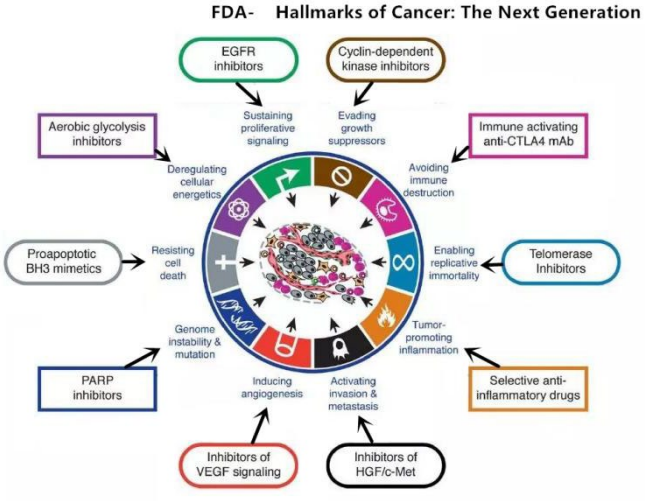

Figure 3: Top Ten Strategies for Targeted Tumor Therapy

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3.1. Multiple kinase inhibitors (Table 1)

Multiple kinase inhibitors inhibit the occurrence and development of tumors through multiple pathways, not only by inhibiting VEGFR and platelet derived growth factor receptors (PDGFR)- β Tyrosine kinase achieves anti-tumor angiogenesis and inhibits tumor growth by regulating the influence of downstream signaling pathways. These drugs include sorafenib, lenvatinib, regofinib, cabozantinib, etc.

3.1.1. Sorafenib

Sorafenib is a novel multi targeted oral drug for the treatment of inoperable or distant metastatic hepatocellular carcinoma. It can act on both tumor cells and tumor blood vessels and has dual anti-tumor effects. It is the first small molecule multi target tyrosine kinase inhibitor (TKI) approved for use in advanced HCC. Sorafenib can inhibit tumor angiogenesis, lymphangiogenesis, and tumor cell proliferation and migration by blocking the activities of VEGFR, PDGFR, FGFR, and Raf family kinases [10-12]. Studies have shown that sorafenib can significantly prolong the median overall survival (OS) of patients with advanced HCC [13-14]. In December 2005, it was approved by the US FDA as a first-line drug for the treatment of advanced renal cancer. In November 2007, the US FDA approved the use of sorafenib for first-line treatment of advanced HCC. However, in clinical treatment, it was found that sorafenib treatment has good tolerance, but the objective effectiveness rate is low, and there are many adverse reactions. The main adverse reactions are controllable diarrhea, rash, fatigue, hand foot syndrome, hypertension, hair loss, nausea, vomiting, and loss of appetite.

3.1.2. Lenvatinib

Lenvatinib is a novel anti-tumor drug, a tyrosine kinase receptor inhibitor that can target signaling pathways such as VEGFR, FGFR, and PDGFR to exert anti-tumor activity [12]. It can also inhibit pathological angiogenesis in other tumors, inhibit tumor growth and disease progression. A phase III clinical study in 2018 found that the median OS of lenvatinib in the treatment of advanced HCC was comparable to that of sorafenib, but the median progression free survival (PFS) and disease progression time (TTP) of lenvatinib were significantly better than those of sorafenib, and lenvatinib had fewer adverse reactions [14]. In 2018, lenvatinib was approved for first-line treatment of mid to late stage HCC. Lenvatinib can also be used in late stage HCC patients with sorafenib intolerance or progression after treatment [15]. After taking lenvatinib, hypertension, proteinuria, nephrotic syndrome, cardiac dysfunction (such as congestive heart failure, cardiogenic shock, and cardiopulmonary failure) may occur Liver toxicity (such as elevated blood bilirubin, elevated aspartate aminotransferase, hepatic encephalopathy), arterial thromboembolism, gastrointestinal perforation and fistula formation, diarrhea, hypocalcemia, and other adverse reactions.

3.1.3. Rigofinib

Rigofinib is a new generation derivative drug of sorafenib, with a chemical structure similar to sorafenib. There is only one fluorocarbon atom on the central benzene ring, but it has stronger inhibitory activity [16]. It is a multi-kinase inhibitor, a new type of anti-tumor drug, and also a molecular targeted drug. It mainly inhibits tumor tissue angiogenesis and tumor metastasis by directly acting on molecular targets on the tumor cell membrane, thus exerting anti-tumor effects. It can be used for the treatment of liver cancer, metastatic colon cancer, etc. Preclinical studies have shown that regofinib can target VEGFR, PDGFR, etc- β, FGFR1, KIT, RET, BRAF, TIE2, etc., inhibit tumor cell proliferation and tumor neovascularization [17]. In 2017, Rigofinib became the first second-line targeted treatment drug approved by the US FDA for late stage HCC that failed sorafenib treatment. The common adverse reactions after treatment with regofinib include arterial hypertension, hand and foot skin reactions, palmoplantar redness and swelling pain syndrome, rash, bleeding, fatigue, myocardial ischemia, infarction, and diarrhea.

3.1.4. Cabozantinib

Cabozantinib is a multi-target small molecule tyrosine kinase inhibitor with high disease control rates for various advanced cancers. It is a small molecule TKI that mainly blocks MET and VEGFR-2, and also has anti AXL, RET, FLT3, KIT activities [18]. In 2018, Abou-Alfa GK et al. [19] found that cabozantinib can significantly prolong the median OS and PFS of advanced HCC patients who progress after sorafenib treatment, significantly improving the objective response rate (ORR). Therefore, cabozantinib is considered to be the preferred second-line targeted treatment drug for advanced HCC patients with sorafenib intolerance. In January 2019, the US FDA approved the use of cabozantinib for second-line targeted treatment of advanced HCC. It is effective for liver cancer, lung cancer, kidney

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cancer, and medullary thyroid cancer, and its control effect on bone metastasis is particularly prominent. The most common adverse reactions are diarrhea, stomatitis, palm-foot redness and swelling syndrome, weight loss, loss of appetite, nausea, fatigue, oral pain, hair color changes, taste disorders, hypertension, abdominal pain, and constipation. The most common laboratory test abnormalities are increased AST, increased ALT, decreased lymphocytes, increased alkaline phosphatase, hypocalcemia, and hyperbilirubinemia.

Table 1: Comparison of Severai Multiple Kinase Inhibitor Drugs

Drugs	Advantages	Disadvantages
Sorafenib	good tolerance	diarrhea, rash, fatigue, hand foot syndrome, hypertension, hair loss, nausea, vomiting, and loss of appetite.
Lenvatinib	inhibit pathological angiogenesis in other tumors, inhibit tumor growth and disease progression.	lenvatinib, hypertension, proteinuria, nephrotic syndrome, cardiac dysfunction
Rigofinib	inhibit tumor cell proliferation and tumor neovascularization	arterial hypertension, hand and foot skin reactions, palmoplantar redness and swelling pain syndrome, rash, bleeding, fatigue, myocardial ischemia, infarction, and diarrhea.
Cabozantinib	high disease control rates for various advanced cancers.prolong the median OS and PFS of advanced HCC patients who progress after sorafenib treatment, significantly improving the objective response rate (ORR).	diarrhea, stomatitis, palm-foot redness and swelling syndrome, weight loss, loss of appetite, nausea, fatigue, oral pain, hair color changes, taste disorders, hypertension, abdominal pain, and constipation. The most common laboratory test abnormalities are increased AST, increased ALT, decreased lymphocytes, increased alkaline phosphatase, hypocalcemia, and hyperbilirubinemia.

3.2. Advantages of Targeted Therapy

Targeted therapy is a selective combination of cellular molecules that directly kills cancer cells without affecting surrounding normal cells. Compared to chemotherapy, targeted therapy is relatively mild and has fewer side effects. Usually, there are symptoms of rash and diarrhea, unlike chemotherapy that can cause hair loss, nausea, and vomiting. It is very suitable for some advanced cancer patients and those who cannot withstand chemotherapy or radiation therapy. Moreover, targeted therapy is very convenient, as patients can take medication directly at home without the need for long-term hospitalization. Moreover, research has found that targeted therapy can effectively prolong the survival time of patients and provide quality of life.

3.3. Shortcomings of targeted therapy

Targeted therapy, as a new way of treating cancer, is very expensive and may not be affordable for some ordinary families. Moreover, there is no guarantee that the targeted treatment will be 100% effective. If there is no effect after treatment, it will cause significant economic damage. Targeted therapy is effective for both early and late stage cancer patients, but not everyone is able to receive targeted therapy, with only one-third of people choosing targeted therapy. Some patients may develop drug resistance. After a period of targeted treatment, the cancer cells in the patient's body gradually become less sensitive to the targeted drug, and the effect of continuing treatment will only worsen, and some may even have no effect at all. For patients who can choose targeted treatment, they cannot be trusted 100%. During the treatment period, patients should pay attention to exercise, strengthen nutrition, and order more fruits and vegetables to improve their immune system, while also maintaining a good psychological state.

4. Summary and Outlook

Liver cancer has a hidden onset and rapid progression, and most patients can only receive systematic treatment. Due to the presence of comorbidities such as hepatitis and cirrhosis, as well as strong heterogeneity, molecular targeted therapy plays an important role. The emergence of multiple multi target molecular targeted drugs and immunomodulatory drugs brings promising prospects for improving the prognosis of patients with advanced liver cancer. When applying these drugs, it is necessary to explore more therapeutic predictive molecules, refer to the design of clinical studies, and try to select the target population that can maximize the benefits. It is important to continue to conduct in-depth research on the pathogenesis and explore potential effective targets, develop new molecular targeted therapeutic drugs, expand the indications of existing molecular targeted drugs, and establish joint medication plans. With the rapid development of high-throughput detection technology and

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continuous research and exploration in molecular biology, it is currently possible to depict the gene molecular map and gene mutations and genomic changes in the disease development process of liver cancer. However, the heterogeneity of liver cancer remains a major challenge in clinical treatment and research. In recent years, with the continuous development of new treatment methods such as molecular targeted therapy and immunotherapy in the field of liver cancer, defining subtypes of patients based on molecular features and exploring biomarkers with clinical significance for efficacy prediction and patient prognosis based on relevant signaling pathways can effectively improve the survival benefits of patients, which is the future development direction of precise treatment and research for liver cancer.

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