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Immune Checkpoint Therapy for Hepatocellular Carcinoma

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Abstract: Globally, chronic hepatitis B virus (HBV) infection is now caused about 60% of the liver cancer. In China, more than 90% of liver cancers are caused by HBV infection. Approximately 800,000 new cases of liver cancer are reported worldwide every year, and the overall prognosis is lack than normal. Most patients with liver cancer suffer from liver diseases such as hepatitis, liver cirrhosis, and abnormal liver function, which cause the onset of liver cancer to be hidden and progress rapidly. The diagnosis is the middle and late stage, and the best opportunity for surgery and other local treatments is lost. The Global Hepatitis Report 2017 released by the World Health Organization shows that more than 325 million people are infected with hepatitis B or C worldwide, and about 1.34 million people die each year. In China, there are about 90 million people with chronic hepatitis B virus, 30 million patients with chronic hepatitis B, and only 2 million people receive treatment, which is less than 1/10 of the total. How to improve the standardized diagnosis and treatment level of liver cancer and optimize the diagnosis and treatment strategy has always been a concern. The liver cancer drug develop is dominated by antibody drugs, of which PD-1/PD-L1 and CTLA-4 are the primary goal of antibody development. The research and development of chemical drugs takes VEGFR and BRAF proteins as the main research targets. At the same time, PD-1 and related drugs that have been on the market have shown good curative effects in a variety of tumor treatments.

1. Introduction

One pf the cancer which is Hepatocellular carcinoma (HCC) is a primary cancer but have high mortality rate and the main histological subtype of liver cancer, accounting for 90% of primary liver cancer. Hepatitis B and C are the two main types of five different hepatitis infections, accounting for 96% of the total mortality from hepatitis. If these hepatitis patients cannot be treated, they will face long-term fatal diseases, including liver cirrhosis and liver cancer.

According to the World Health Organization, these tumors include: hepatocellular carcinoma (HCC), Cholangiocarcinoma, Bile Duct Cystadenocarcinoma, Combined Hepatocellular and Cholangiocarcinoma, Hepatoblastoma, Undifferentiated Carcinoma (1). Among them, HCC accounts for about 90% of primary liver cancer. Therefore, existing liver cancer therapies and research therapies are mainly carried out around HCC.

Approximately 800,000 liver cancer new cases are reported worldwide every year, and the overall prognosis is poor. The 5-year net survival rate of liver cancer from 2000 to 2014 in 61 countries and

regions worldwide was 5-30% (2). Most patients with liver cancer suffer from liver diseases for example hepatitis, liver cirrhosis, and abnormal liver function, which cause the onset of liver cancer to be hidden and progress rapidly. The diagnosis is the middle and late stage, and the best opportunity for surgery and other local treatments is lost. Statistics updated as of December 31, 2015 show that the 5-year survival rate of liver cancer patients in my country is only 12.1% (3), which is significantly lower than that of neighboring Japan.

According to the global and Chinese cancer statistics in 2018, combined with the GLOBCAN 2018 global cancer data online database of the International Union Against Cancer (UICC), in 2018, liver cancer was the fourth most familiar malignant tumor in China (the age-standardized rate was 18.3 people per 100,000 People) and the third cause of tumor death (age-standardized rate of 17.1 people per 100,000 people). The incidence of liver cancer ranks fourth among Chinese men, with an age-standardized rate of 27.6 people per 100,000, and the second-ranked fatality rate among men, with an age-standardized rate of 25.6 people per 100,000. For Chinese women, the relevant data None of them are in the top five. The incidence and mortality of liver cancer among Chinese men are much higher than those of women, which may be related to drinking or smoking habits (4-6).

The drug development of liver cancer is mainly of antibody drugs, which is PD-1/PD-L1 and CTLA-4 are the main targets of antibody development. The research and development of chemical drugs takes VEGFR and BRAF proteins as the main research targets.

2. Sorafenib

Currently, liver cancer drugs on the Chinese market can be divided into two categories: chemotherapeutics and targeted drugs. Targeted drugs target specific molecules related to cancer in the cell signaling pathway, including small molecule targeted drugs and monoclonal antibodies. Targeted drugs that are effective for liver cancer, such as Sorafenib, Regorafenib, and Lenvatinib, are all multi-target drugs.

Sorafenib (Nexavar) was developed by Bayer and was approved by the US FDA in 2005. It is the world's first oral multi-target kinase inhibitor approved for marketing (7). The drug was approved to enter China in 2006 under the trade name Nexavar. It is used for the patient in the first-line treatement with inoperable advanced liver cancer. The drug directly inhibits tumor growth by inhibiting the Raf/Mek/Erk signaling pathway, and indirectly inhibits tumor growth by blocking the formation of tumor blood vessels by inhibiting VEGFR and PDGFR. Sorafenib's global sales peaked in 2015 and have since continued to decline due to the impact of competing products. In 2018, global sales of 712 million euros, a year-on-year decrease of 14.63%. Before Sorafenib entered China's medical insurance, the high drug cost of about 50,000/month restricted its clinical use. After being included in the national medical insurance catalog in July 2017, the cost was reduced to about 10,000/month, realizing an increase in the amount. In 2018, the sales of China's sample hospitals were 361 million yuan, a year-on-year increase of 85%.

According to the SHARP study of a multi-center, double-blind, placebo-controlled phase III clinical study conducted in Europe and the United States (8), the median OS (overall survival) of patients in the medication group was longer than that in the placebo group, 10.7 months vs 7.9 months, But ORR (Objective Response Rate) is low, only 2%. According to the multi-center, double-blind, placebo-controlled phase III clinical study ORIENTAL in the Asia-Pacific region (9), the median OS of patients in the medication group was longer than that in the placebo group, 6.5 months vs 4.2 months. Sorafenib increases the risk of diarrhea, weight loss, hand-foot skin reactions, and hypophosphatemia. Targeted drugs that emerged after sorafenib, such as cetuximab, bevacizumab, lapatinib, sunitinib, ramucirumab, etc., are head-to-head with sorafenib in the trial, the primary endpoint OS was not better than sorafenib, or the trial was terminated early due to serious adverse events. Although sorafenib can only prolong the median overall survival of about 3 months and has

safety issues, it is still the only drug used for systemic treatment of advanced hepatocellular carcinoma in the past ten years. Sorafenib's compound patent has expired in January 2020, and the crystal form patent will expire in September 2025.

3. PD-1 and CTLA-4

At present, 8 PD-1/PD-L1 monoclonal antibodies have been listed in the Chinese market, including 2 imported PD-1 monoclonal antibodies, 2 imported PD-L1 monoclonal antibodies, and 4 domestic PD-1 monoclonal antibodies. Under the fierce competition, expanding indications and combination medications are obvious strategies. Liver cancer is a major indication in Chinese tumors, and the curative effects of existing chemotherapy and targeted therapies are limited, and there are many unmet clinical needs. Naturally, it has become a battleground for all families. At present, 12 PD-(L)1 monoclonal antibodies have carried out clinical trials on liver cancer indications in China, involving first-line to third-line treatment and adjuvant therapy, including 4 monoclonal antibodies (Fuhong Henlius, Kangfang Biological, Zhengda Tianqing, Yuheng Pharmaceutical) have not been approved for any indication in China.

In March and June 2020, Hengrui issued an announcement stating that Carrelizumab (the trade name Erika) has been approved for new indications for monotherapy and has received sorafenib treatment and/or contains Oxafen. Patients with advanced hepatocellular carcinoma undergoing Liplatin system chemotherapy became the first PD-1 monoclonal antibody approved for liver cancer indications in China. The second-line treatment of advanced HCC is the second indication approved by Hengrui PD-1 monoclonal antibody which in China after the third-line treatment of relapsed or refractory classic Hodgkin lymphoma (r/r cHL) was approved in May 2019.

In China, it is not to be proved that OK drugs is liver cancer instuctions, but they have been approved in the United States. BMS's O drug (Nivolumab) was approved by the US FDA for the second-line treatment of hepatocellular carcinoma (HCC) in September 2017 based on the data of the Phase I/II clinical study CheckMate040. Merck’s K drug (Pembrolizumab) was approved by the FDA for the treatment of HCC patients who had been treated with sorafenib in November 2018 with the data from the phase II clinical study KEYNOTE-224.

For CTLA-4, it is targeted monoclonal antibody, the TTP (Time to Progress) of it is about6.46 month. And OS (Overall Survival) of it is about 8.2 month. So how do the CTLA-4 works. When combined with CD80 or CD86 on the surface of antigen-presenting cells, it acts as a "off" switch. CTLA-4 binds CD80 and CD86 with greater affinity and affinity than CD28, so it can surpass the ligand of CD28 (10). CTLA4 transmits inhibition signal to T cells, while CD28 transmits stimulation signal. CTLA4 is also found in regulatory T cells and contributes to their inhibitory function. CTLA-4 expression is increased by T cell activation via T cell receptor and CD28 (11).

CTLA-4 actually can be used with PD-1 which can help the sorafenib that let the OS of the patient rise to about 23 month which is a very big progress, for the treatment of the liver cancer.

Anti-PD-1 can also be used with other kind of antibody drugs like anti-VEGF axis targeting drugs, Regorafenib is one of its which is now used as second line therapy for advanced HCC patients with sorafenib failure. Anti-PD-1 is an immunosuppressive molecule which will control the T-cells, normally it helps our body but it will prevent our body system to attack the cancer cell, in order to cure the cancer, it is important to let the PD-1 be stopped. So, the scientist invents the medicine which can control or kill PD-1, let our body itself to attack the cancer cell. In vitro, treatment of anti-CD3 stimulated T cells with PD-L1-IG resulted in T cell proliferation and IFN- γ the secretion decreased (12). IFN- γ it is a key pro-inflammatory cytokine that advanced the inflammatory activity of T cells. Reduced T cell proliferation was also associated with reduced IL-2 secretion, and together the data come from the scientist suggest that PD-1 is non-positive regulates T cell response (13). However, using this medicine might cause interstitial pneumonia or immune pneumonia can also cause immune

enteritis. Which means some of the patient cannot be able to use this kind of medicine to defend the cancer in their body. When it activates the autoimmune response, it may also activate the antibody response at the same time. So actually, some people can't use it for a long time. Using it also means we need to check what cancer we need to cure because it cannot target correctly. What's more, PD-1 sometimes don't be react correct. The doctor is required to distinguish between the medicines. Even if PD-1 and PD-L1 are expressed in T cells and tumor tissues, the therapeutic effect is sometimes not ideal, and it is usually associated with lack of INF- γ it is related to inflammation. In some patients, PD-1 was expressed on T cells, and PD-L1 was also expressed in tumor tissues- γ When the expression of PD-1 was low and there was no inflammation, there was almost no effect of PD-1 and PD-L1 mAbs. At this condition we may consider to artificially guided inflammation to let the treatment be more effective. so, what about how we get to know PD-1? The median OS was 26.3 months in the K medicine group and 13.4 months in the first-line treatment group. In the control group, 55% of the patients crossed to the K group, and 11% of the patients received other PD-1 / PD-L1 mAbs, the risk of death was reduced by 38%; The OS rates at 60 months were 31.9% and 16.3%, respectively, which means that the 5-year OS rate of the K-drug monotherapy group is nearly twice that of the platinum-based chemotherapy group, and nearly one-third of the patients are still alive at 5 years.

4. Discussion

The limited number of liver cancer targeted drugs on the market is due to the difficulty in new drug research and development, which is mainly caused by three factors. Firstly, different from non-small cell lung cancer, which has clear driving genes (such as EGFR, KRAS, ALK, ros1, etc.), no clear liver cancer driving genes have been found at present, with obvious heterogeneity, except that c-met (tyrosine protein kinase met or hepatocyte growth factor receptor HGFR) may play a relatively important role. At present, the effective targeted drugs for liver cancer, such as sorafenib, Regofinib and Renvatinib, are multi-target drugs. Secondly, liver cancer is closely related to infection. Patients usually have liver diseases such as hepatitis B and hepatitis C, which raise higher requirements for the safety of liver cancer drugs. Finally, the global liver cancer is concentrated in China and relatively few in developed countries with strong new drug research and development capabilities, resulting in relatively limited enthusiasm and investment in liver cancer drug research and development.

The current global drug development for HCC is dominated by checkpoint (PD-1, etc.) inhibitors, but the combination of immune checkpoint inhibitors and chemotherapy/targeted drugs is increasingly prominent, such as the brilliant "T +A" combination, namely PD-L1 monoclonal antibody Tecentriq (Aezolizumab) + Avastin (Bevacizumab). The small-molecule targeted drugs for liver cancer are mostly multi-target inhibitors such as VEGFR, FGFR, PDGFR, and c-Met.

Domestic head R&D companies such as Hengrui, Junshi, Cinda, Baiji, etc. all regard liver cancer as a key indication area, and have carried out PD-1 monoclonal antibody monotherapy or combination drugs as various line of treatments for the treatment of liver cancer.

In 2021, according to the clinical trial website, there were 18 clinical trials of TCR-T in the treatment of HCC and 27 clinical trials of CAR-T in the treatment of HCC, including 18 clinical trials of CAR-T cells targeting GPC3 in the treatment of HCC.

In the future, there may be cases where multiple products get together and approved for liver cancer indications. The survival treatment of liver cancer patients will be greatly improved. With the continuous improvement and development of technology, it can even be expected that many solid tumors have the possibility of curing.

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