Review

Current strategies of precision medicine on advanced liver cancer

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Liver cancer is one of the most common malignancies with the sixth highest incidence rate and the second highest mortality among the death spectrum of cancers worldwide. Most often, liver cancer patients are usually in their advanced stages that have lost the chance of surgical resection upon the diagnosis. Precision treatment is a newly emerging concept for the treatment of human diseases with accuracy and efficacy by using patient information at genomic and proteomic levels. Based on clinical characteristics and mutant status of driver gene, the disease may be divided into different categories that can be individually studied by using a specific therapeutic target, therefore, formulating a reasonably and efficiently personalized treatment strategy. This review is mainly focused on the most recent progress on the precision treatment of advanced liver cancer, especially on the strategies based on the disease-related mutant genes and current status of the targeted drugs used in clinical precision treatment in liver cancer.

Key Words: Liver cancer; Gene; Precise medicine; Molecular targeted therapy; Drug

INTRODUCTION

Liver cancer is one of the common malignant tumors of the digestive system, including hepatocellular carcinoma (HCC), cholangiocarcinoma and mixed hepatocellular carcinoma, of which about 90% are HCC.¹ The incidence and mortality of liver cancer rank sixth and fourth in the world, respectively.² In 2012, 782,000 people were diagnosed with liver cancer, and 746,000 people die from this disease worldwide.³ The overall incidence of cancer has been decreased by about 0.7% per year, but the incidence of liver cancer has been continuously rising from 2003 to 2012 in some developed countries including the United States.⁴ China has the highest incidence rate of liver cancer in the world that may account for about 50% of the total cases.^{5,6} The risk factors include hepatitis virus infection, nonalcoholic fatty liver, excessive alcohol consumption and aflatoxin B1 treatment.^{7,8} In developed world such as Europe, America and Japan, hepatitis C cirrhosis is the major cause of about 60-70% liver cancer.⁹ Currently, the conventional therapies for liver cancer mainly include liver transplantation, hepatectomy, radiotherapy, chemotherapy, percutaneous ethanol injection, radiofrequency ablation, transcatheter arterial chemoembolization (TACE) and

targeted therapy.^{10,11} However, most liver cancer patients are in their advanced stage upon diagnosis.¹² The effects of these conventional therapies are usually not satisfactory and even result in very poor prognosis.¹³ Among them, liver transplantation is currently the best curative option to treat liver cancer that is followed by surgical resection. In TNM stage I HCC patients the median survival for liver transplantation and hepatectomy were 127.9 and 56.7 months, respectively ($P < 0.0001$), while the postoperative risk of tumor recurrence is high.¹⁴⁻¹⁶ Therefore, there is an urgent need to develop a precise therapy plan suitable for patients with either preoperative advanced HCC or

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postoperative recurrent HCC.

Up to now, FDA-approved targeted drugs for advanced liver cancer include first-line Sorafenib and second-line Regorafenib.¹⁷ In clinical studies, Sorafenib appears to be well tolerated and has antitumor activity, but the median overall survival (mOS) is only 12.3 months.¹⁸ Patients taking Sorafenib are prone to have serious adverse effects, such as gastrointestinal bleeding, severe hand-foot syndrome, as well as reduced quality of life.^{19,20} About 25 molecularly targeted drugs have been undergone phase III clinical trial in HCC patients from 2007 to 2015, but no clinically effective drug has been found to be superior to Sorafenib.²¹⁻²⁷ In 2017, a phase III clinical trial on Lenvatinib for patients with unresectable HCC was reported at the ASCO annual meeting. The study found that Lenvatinib was superior to Sorafenib in the treatment of advanced liver cancer (mOS: 13.6 months vs. 12.3 months)¹⁸ but with no statistical difference. Recent reports show that Lenvatinib is, in fact, neither inferior nor superior to Sorafenib, and can be considered as a long searched first line drug for the alternative of Sorafenib. Even though, drug treatment for advanced liver cancer is still in its shortboard. This review summarizes the recent progresses of precision medical research on advanced hepatocellular carcinoma, especially focusing on the updated progress on the molecular targeted therapy for advanced HCC.

THE CONCEPT OF PRECISION TREATMENT

Precision medicine has been become an important and emerged direction pursued by people from both basic research and clinical medicine. The precision medicine is tightly related to the detailed sequence information generated from both the human gene and genome. The genetic information can be more easily deciphered than five years ago since the fast innovations of sequencing technology have let the individual diagnosis and treatment become possible. Precision treatment is centered on the elucidation of gene mutations critical to the diseases, especially the driver mutations. HCC is a heterogeneous disease that usually carries multiple genetic mutations or epigenetic changes²⁸ which may often result in poor efficacy when a common treatment is applied. The precise medical treatment of HCC is based on the gene sequencing results of the patient and can be divided into different sub-categories. Individualized treatment plans should be developed by following the individual sub-category as a guide to control disease progression, to prolong survival time and eventually to improve the quality of life.^{29,30}

LIVER CANCER RELATED SOMATIC MUTATIONS

Studies show that the genetic and epigenetic changes of several critical genes were associated with the development of liver cancer.^{31,32} The telomerase reverse transcriptase (TERT) gene promoter mutation is a common somatic genetic variant in HCC, which is present in 50% of HCC patients.³³ Telomerase reverse transcriptase is an enzyme that is necessary for telomere elongation and preventing cell damage. The correlation between TERT promoter mutation and hepatocarcinogenesis suggests that it may be a potential target for liver cancer treatment.^{34,35} It was found that telomere shortening was significantly associated with patient survival and disease recurrence in liver cancer.³⁶ As a common tumor suppressor gene, TP53 gene was found to be functional absence in about 50% of malignant tumors.³⁷ About 28% of liver cancer patients carry TP53 gene mutation which is the second

common mutation observed in liver cancer.³⁸ TP53 regulates various cellular stress responses such as cell cycle arrest, apoptosis and DNA repair, and maintains the normal function of the body.³⁹ TP53 gene also regulates VEGF-A gene. Studies have shown that the efficacy of anti-angiogenic drugs is associated with the presence of TP53 mutations in tumor patients.⁴⁰ The CTNNB1 gene, also known as the β -catenin gene, encodes the β -catenin protein that plays a key role in the WNT signaling pathway.⁴¹ Numerous studies have shown that CTNNB1 gene mutation results in the abnormal activation of the WNT signaling pathway which may directly promote tumorigenesis.⁴² In addition, double mutations at the TERT promoter and CTNNB1 gene have been found in a small cohort of HCC patients, indicating that liver cancer can be a disease with multiple genetic abnormalities.⁴³ However, the significance of the double mutations in the clinic is still needed to be further explored. About 10% of HCC patients carry ARID1A gene mutation. ARID1A is a subunit of SWI/SNF complexes which is one of the important complexes of chromatin remodeling. ARID1A mutation reduces the transcription of tumor suppressor genes and increases the risk of HCC.^{31,32} Studies showed that loss function of ARID1A gene is associated with the development of many cancers such as kidney cancer, liver cancer and breast cancer. Further analysis also showed that ARID1A gene mutation was located at the opposite stand of the genome to that of TP53 gene mutation, indicating that both ARID1A and TP53 may jointly inhibit tumor formation. Similar to ARID1A gene, approximately 5-10% of patients with liver cancer have the ARID2 gene mutation, while ARID2 is also a subunit of the SWI/SNF complexes.^{31,32} Overall, the TERT gene, TP53 gene, CTNNB1 gene, ARID1A gene and ARID2 gene are the most common mutated genes that are closely related to the development of liver cancer.

Common somatic copy number alterations include focal amplification at chromosome 11q(CCND1 and FGF19), 7q(MET) and 6p(VEGFA) in liver cancer.⁴⁴ The study demonstrated that up-regulated expressions of epidermal growth factor receptor (EGFR) were found in 66% of liver cancer patients.⁴⁵ However, the up-regulated EGFR expression was mainly due to polysomy with extra chromosome 7 but not due to copy number changes in EGFR. The drug erlotinib is usually used in the clinic to treat HCC by specifically inhibiting EGFR. Other pathways such as mTOR and TGF- β may also be considered as potential therapeutic targets. The study by Zhang et al. demonstrated that Sorafenib effectively inhibited the progression of liver cancer by down-regulating the expression of PI3K/AKT/mTOR signaling pathway,⁴⁶ while microRNA-449 family inhibits TGF- β -mediated liver cancer cell migration by targeting SOX4.⁴⁷

Currently, newly discovered molecular markers related to liver cancer include SPAG9/MKK3/p38 axis, AKR1C3, B3GAT3, DYRK2 and BPTF.⁴⁸⁻⁵² The study showed that down-regulation of Spermin-associated antigen 9 (SPAG9) can reduce the expression of MKK3 and p38 proteins, inhibits cell proliferation and promotes cell apoptosis. Therefore, SPAG9 may be a potential new target for liver cancer treatment.⁴⁸ In addition, it was found that AKR1C3 is an independent biomarker for the prognosis of liver cancer by database mining. However, the expression level of AKR1C3 was inversely correlated with the overall survival of liver cancer patients.⁴⁹ Experimental studies showed that high level of B3GAT3 expression is associated with patients' poor prognosis.⁵⁰ Currently, many molecular markers related to the diagnosis and prognosis of liver cancer have been discovered by people via experimental studies, big data analysis and other methods.

VEGF, FGF AND PDGF-TARGETED THERAPY FOR HCC

In 2006, the emergence of Sorafenib changed the state of long lack of targeted drugs for liver cancer treatment. Sorafenib is an oral multiple kinase inhibitor that mainly targets several signaling molecules such as VEGFR2, PDGFR and Ras/MAPK.⁵³ The interactions between VEGFR2 and several ligands (VEGF-A, VEGF-C and VEGF-D) are important for the process of angiogenesis. As a common mutation gene in liver cancer, TP53 can regulate VEGF-A gene expression. The clinical trial also showed that Sorafenib can control disease progression and prolong the survival of advanced liver cancer patients.⁵⁴ The SHARP study was a randomized, double-blind, multicenter study that included 602 advanced liver cancer patients. The primary endpoints were overall survival (OS) and the time to symptomatic progression (TTSP), while the secondary endpoints were time to progression (TTP) plus disease control (DC). The results showed that the mOS of the Sorafenib group and the placebo group were 10.7 months vs. 7.9 months (HR=0.69, 95% CI: 0.5 to 0.87; $P=0.0006$), respectively, while TTP was 5.5 months vs. 2.8 months (HR=0.58, 95% CI: 0.45 to 0.74; $P=0.00007$), respectively.⁵⁴ In addition, Oriental studies also showed that the Sorafenib group prolonged OS as compared with placebo in advanced liver cancer patients in the Asia-Pacific region with mOS were 6.5 months vs 4.2 months (HR=0.68, 95% CI: 0.50~0.93), respectively.⁵⁵ Based on the SHARP and Oriental studies, the U.S. Food and Drug Administration (FDA) approved Sorafenib as a first-line drug for advanced liver cancer.

A randomized phase III trial to compare the OS of Sunitinib vs. Sorafenib was conducted in a cohort of 1074 patients with advanced liver cancer.²¹ All patients were randomized into the Sorafenib group and Sunitinib group. Sunitinib targets VEGFR1-3, PDGFR α/β , FLT3, c-Kit and RET.⁵⁶ The results showed that the mOS of the Sorafenib group was 10.2 months and the mOS of the Sunitinib group was 7.9 months (HR=1.30; one-sided $P=0.9990$; two-sided $P=0.0014$). Further subgroup analysis showed that the mOS of the Sorafenib group and the sunitinib group were

7.7 month vs. 8.8 months in the Asian population, respectively (HR=1.21; one-sided $P=0.9829$). The survival time of the Sunitinib group was not significantly improved, but the incidence of adverse events was increased by 13.3% vs. 12.7% in the Sunitinib group vs. Sorafenib group, respectively.²¹

Another randomized phase III trial has also been conducted to compare the dual inhibitor Brivanib with the multiple inhibitor Sorafenib as the first line treatment for advanced liver cancer. The randomized phase III BRISK-FL study showed that Brivanib is effective as compared with the control group (Sorafenib group).²² Brivanib is selectively acting on fibroblast growth factor 2 (FGF-2) and vascular endothelial growth factor (VEGF) signaling pathway.⁵⁷ The study showed that the mOS of Sorafenib group and Brivanib group 9.9 months vs. 9.5 months (HR=1.06; 95.8% CI, 0.93-1.22), respectively. The TTP was similar in the two groups, but adverse event rates were higher in the Brivanib group. There was no significant advantage compared with the Sorafenib group.²²

In addition, some clinical trials using other targeted drugs such as Erlotinib (inhibitors for epidermal factor receptor) combined with Bevacizumab (humanized monoclonal antibody against vascular endothelial growth factor),⁵⁸ Cediranib (ALK translocation),⁵⁹ Dovitinib (inhibitor for fibroblast growth factor receptor 3)⁶⁰ have also been tested as the potential first-line treatment for advanced HCC (Table 1). However, none of them have exceeded the efficacy of Sorafenib. Importantly, recent clinical studies have recovered several candidate drugs that may potentially replace Sorafenib as a first line drug in the clinic.⁶¹ In a multicenter clinical trial,⁶² Nintedanib (multiple inhibitors for VEGFR1/2/3, FGFR1/2/3 and PDGFR α/β) can prolong the survival of advanced liver cancer patients in Europe with a better clinical curative effect than that of Sorafenib. Levatinib, as a multiple inhibitors by targeting VEGFR1-3, RET, FGFR (1-4), c-KIT, PDGFR- α and PDGFR- β ,⁶³ has high efficacy in anti-angiogenesis and anti-tumor cell proliferation. The study has shown that the median survival time, overall survival time and progression-free survival time of the Levatinib group were superior to that of the Sorafenib group.⁶⁴

Table 1. Clinical trial of drug therapy by targeting VEGF, FGF and PDGF for advanced liver cancer*

Author (publish years)	Drug	Target	Phase	No. (male / female)	Primary end point	P	Reference
Llovet JM,et al (2008)	Sorafenib vs. Placebo	VEGFR2/PDGFR/Ras/MAPK	III	602 (524/78)	mOS (10.7m vs.7.9m)	$P<0.001$	54
Abou-Alfa GK,et al (2010)	Sorafenib+Doxorubicin vs. Doxorubicin/Placebo	VEGFR2/PDGFR/Ras/MAPK	II	96 (73/23)	mOS (13.7m vs. 6.5m)	$P=0.006$	65
Cheng AL,et al(2009)	Sorafenib vs. Placebo	VEGFR2/PDGFR/Ras/MAPK	III	226 (33/193)	mOS (6.5m vs.4.2m)	$P=0.014$	55
Cheng AL, et al(2013)	Sunitinib vs. sorafenib	VEGFR1-3/PDGFR α/β /FLT3/c-Kit/RET vs. VEGFR2/PDGFR/Ras/MAPK	III	1074 (895/179)	mOS (7.9m vs. 10.2m)	$P=0.0014$	21
Zhu AX,et al(2015)	Sorafenib + erlotinib vs. Sorafenib + Placebo	VEGFR2/PDGFR/Ras/MAPK	III	720 (581/139)	mOS (9.5m vs. 8.5m)	$P=0.408$	24
Ciuleanu T(2016)	placebo-sorafenib vs. mapatumumab-sorafenib	VEGFR2/PDGFR/Ras/MAPK	II	101 (65/36)	mTTP (5.6m vs.4.1m)	$P=0.30$	66
Kudo M,et al(2018)	Lenvatinib vs. sorafenib	VEGFR (1-3), RET, FGFR (1-4), c-KIT, PDGFR- α and PDGFR- β vs. VEGFR2/PDGFR/Ras/MAPK	III	954 (806/148)	mOS (13.6m vs. 12.3m)	/	61

*The clinical trial data was obtained from ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/home>), searching for "liver cancer" or "hepatocellular carcinoma" as keywords, clinical trials with a number of cases of not less than 25 and following the standard of case-control design were listed. Some trials progress due to a high incidence of serious adverse reactions, which are not listed in this table; mOS:median overall survival time; OS:overall survival time; PFS:Progress-free survival; mTTP:median time to progression.

In 2017, Regorafenib was approved by the FDA as the second-line setting for advanced liver cancer treatment. Regorafenib is also a multi-targeted receptor tyrosine kinase inhibitor by targeting rRET, C-RAF, VEGFR2, c-Kit, VEGFR1 and PDGFR β . Regorafenib could be used for the treatment of advanced liver cancer with acquired sorafenib resistance.⁶⁷ The RESORCE study included 573 patients with advanced liver cancer who were randomly assigned to the regorafenib group (160 mg/d) and placebo group. The results showed that the median survival time (from the start of treatment with Sorafenib to the time of death) was 26.0 months after regorafenib treatment vs. 19.2 months after placebo treatment.⁶⁸ In addition, the efficacies of many other second line drugs for HCC patients were

listed in Table 2. The BRISK-PS study showed that mOS was 9.4 months vs. 8.2 months (HR=0.89, 95.8% CI: 0.69-1.15; $P=0.3307$) in the Brivanib group and placebo group, respectively. Brivanib is dual inhibitor of VEGF and FGFR. However, there was no significant improvement in the prognosis of patients in Brivanib group.²⁵ A phase III double-blind, randomized, controlled trial showed that the OS of advanced HCC patients were 7.8 months vs. 4.2 months (HR 0.67; 95% CI 0.51-0.90) in the second-line treatment of Ramucirumab vs. Placebo, respectively.⁶⁹ Ramucirumab is a specific inhibitor for VEGFR2.⁷⁰ It has been demonstrated that the application of Ramucirumab as second-line treatment drug did not significantly improve the survival rate of patients with advanced HCC.

Table 2. Clinical trial on second-line treatment of liver cancer*

Author (publish years)	Drug	Target	Phase	N (male / female)	Primary end point	P	Reference
Zhu AX,et al(2016)	Everolimus vs.Placebo	mTOR	III	546 (463/83)	mOS (7.6m vs. 7.3m)	$P=0.01$	71
Zhu AX,et al(2015)	Ramucirumab vs.Placebo	VEGFR2	III	565 (478/87)	mOS (9.2m vs. 7.6m)	$P=0.14$	69
Kang YK,et al(2015)	Axitinib vs.Placebo	VEGFR1-3	II	224 (183/41)	mOS (12.7m vs. 9.7m)	$P=0.287$	72,73
Bruix J,et al(2017)	Regorafenib vs.Placebo	r RET/C-RAF/VEGFR2/ c-Kit/VEGFR1/PDGFR β	III	573 (504/69)	mOS (10.6m vs. 7.8m)	$P<0.0001$	67
Abou-Alfa GK,et al(2018)	Cabozantinib vs.Placebo	MET/ VEGF/ AXL /RET	III	707 (5581/126)	OS (10.2m vs. 8.0m)	$P=0.005$	73

*The clinical trial data was obtained from ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/home>), searching for "liver cancer" or "hepatocellular carcinoma" as keywords, and clinical trials with a number of cases of not less than 25 and following the standard of the case-control design were listed. Some trials were terminated due to a high incidence of serious adverse reactions, which are not listed in this table; mOS: median overall survival time; OS: overall survival time.

Surgery can be a curative treatment for liver cancer when cancer is a single foci with less than 1cm. However, HCC recurrence may exhibit in some postoperative patients.⁷⁴ A phase III, randomized, double-blind, placebo-controlled trial indicates that Sorafenib is not an effective intervention for hepatocellular carcinoma following resection or ablation. The median recurrence-free survival (mRFS) were 33.3m vs. 33.7m (HR=0.940; 95% CI 0.780-1.134; one-sided $P=0.26$) in the Sorafenib and placebo group, respectively.⁷⁵ Liver transplantation is the best choice for liver cancer patients who are within Milan criteria. Its 5-year survival rate is significantly higher than that of liver resection.¹⁴⁻¹⁵ However, some patients still have tumor recurrence after liver transplantation. Currently, the recipients of liver transplantation with HCC recurrence were usually treated with Sorafenib. The median survival time of the Sorafenib-treated group was better than that of the best supportive care group (median, 14.2 vs. 6.8 months; $P=0.01$).⁷⁶ Moreover, clinical study demonstrated that the combined treatment with Sorafenib and Everolimus may improve the prognosis of liver transplantation recipients with HCC recurrence.⁷⁷

mTOR-TARGETED THERAPY ON HCC

Mammalian target of rapamycin (mTOR), a typical serine/threonine kinase, is an important target for cancer treatment. mTOR is downstream and can be activated by PI3K/Akt signaling pathway. The upstream signaling molecules in PI3K/Akt/mTOR include EGFR, MET, HER2 and FGFR. The deregulation of PI3K/Akt/mTOR signaling pathway can be caused by mutations at PI3K, AKT or PTEN, which will have direct effects on cell

proliferation, cell apoptosis and cell motility. mTOR inhibitor includes Sirolimus and Everolimus that can be used as anti-rejection drugs after organ transplantation. The EVOLVE-1 randomized clinical trial employed Everolimus as a second-line drug for the treatment of advanced liver cancer patients, 303 deaths (83.7%) in the Everolimus group and 151 deaths (82.1%) in the placebo group (HR= 1.05; 95% CI, 0.86-1.27; $P=0.68$). The mOS of Everolimus group and placebo group were 7.6 months vs. 7.3 months, respectively. The results showed that Everolimus did not significantly improve the overall survival of patients with advanced HCC.⁷¹ A randomized multicenter, multinational phase II trial showed that Sorafenib plus Everolimus were not superior to Sorafenib alone. PFS (6.6 vs. 5.7months), TTP (7.6 vs. 6.3months) and OS (10 vs. 12months) were similar in the Sorafenib group and Sorafenib plus Everolimus group,⁷⁸ respectively. Bhooori et al. reported that a 46-year-old female liver cancer patient was diagnosed as recurrence after liver transplantation. Immunohistochemical staining showed that β -catenin (Wnt pathway), pERK (Ras/MAPK pathway) and pS6 (Akt/mTOR pathway) were positive. After treatment with Sorafenib for 3 months, the mTOR inhibitor, Everolimus was added orally as 1.5 mg bid. Since Everolimus has both anti-tumor and immunosuppressive effects, the Cyclosporine was withdrawn. After 3 months of combination therapy, the tumor was reduced by 50%. After 6 months, the tumor was further reduced by more than 50%.⁷⁹

Bigelovin (BigV) is a sesquiterpene lactone, which inhibits the proliferation of HepG2 cells and induces apoptosis of HepG2 cells via mTOR signaling pathway. Bigelovin may have the potential to be developed as a new anti liver cancer drug.⁸⁰ The study also reported that Ponatinib, a protein tyrosine kinase inhibitor, could

induce G1 cell cycle arrest and promoted the apoptosis of both SK-Hep-1 and SNU-423 cells by up-regulating the expressions of cleaved caspase-3 and caspase-7. Blocking mTOR signaling pathway could further enhance the anti-tumor activity of Ponatinib.⁸¹

cMET-TARGETED THERAPY ON HCC

Studies showed that the deregulation of cMET activity could be related to the development of HCC.⁸² c-Met is a receptor tyrosine kinase that can be recognized by hepatocyte growth factor (HGF). The interaction between c-Met and HGF is critical for hepatocyte survival.⁸³ c-Met promotes tumor angiogenesis by affecting VEGF-A expression.⁸⁴ Cabozantinib is c-Met inhibitor. One study reported that Axitinib plus Cabozantinib can treat advanced HCC patients who fail with Sorafenib treatment. Although the combined treatments were effective, the case developed acute hepatic and renal damage.⁸⁵ Cabozantinib can be served as second line drug to treat the patients who are insensitive to Sorafenib or other standard treatments. This randomized, double-blind, phase III trial conducted by Bruix et al. demonstrated that the Cabozantinib group had longer OS and PFS than that of the placebo group. However, the adverse events were higher in the Cabozantinib group.⁸⁶ An HCC patient with bone metastasis was treated with Sorafenib plus radiofrequency ablation. However, bone metastasis still occurred after two months of treatment. In order to prolong the patient's life, whole exome sequencing was performed. The results showed that MET gene was amplified in the patient, indicating that MET gene was likely the potential therapeutic target. Subsequently, the patients was treated with the MET inhibitor Tepotinib and had a complete response for 14 months.⁸⁷ In addition, experimental studies have also found that ginkgolic acid may become a new liver cancer chemotherapy drug, which inhibits HepG2 cell invasion by down-regulation of HGF/c-Met signaling.⁸⁸

ANTI IMMUNE CHECKPOINT AND ADOPTIVE THERAPIES ON HCC

The strategy of the immune checkpoint blockade has been applied for the treatment of HCC. The clinical trial conducted by El-Khoueiry et al. showed that Opdivo (anti-PD1) can prolong OS in HCC patients when treatment with Sorafenib was failed.⁸⁹ In 2017, FDA approved Opdivo as a first-line drug for liver cancer patients who were previously treated with Sorafenib. Another study on Tremelimumab (anti-CTLA-4) showed that patients taking Tremelimumab can achieve partial response rate with the tumor control rate being 76.4%.⁹⁰ Another randomly clinical trial showed that adoptive immunotherapy can reduce HCC recurrence. The OS rate in 5 years was 74% vs. 62% in adoptive immunotherapy vs. control groups, respectively.⁹¹ Moreover, the study demonstrated that GPC3 may be a potential target of immunotherapy on HCC due to its deregulated expressions in most of HCC tissues as compared with that of the normal controls.⁹² A study showed that GPC3 vaccination indeed achieved a partial response. The OS has significant differences between the high (N=15) and low (N=18; P=0.033) GPC3-specific CTL frequencies.⁹³ Therefore, further research is needed to identify sensitive populations for the above immunotherapies.

CONCLUSION

The liver cancer patients are usually at their late-stage upon

diagnosis. Effective treatments are urgently demanded this type of cancer. Most of the patients will lose their chances of liver resection mainly due to their large tumor sizes with multiple foci metastasis. This type of HCC usually has a higher recurrence rate even after hepatectomy. Liver transplantation can offer a complete cure for the advanced HCC, but the limited liver resources has restricted the development of this strategy. Hence, improving the prognosis and prolonging their survival time has always been the most important clinical consideration. The emergence of precision medicine has brought advanced HCC patients with more hopes.

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