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TOPIC HIGHLIGHT

2016 Hepatocellular Carcinoma: Global view

Progress in systemic therapy of advanced hepatocellular carcinoma

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Abstract

Primary liver cancer, mainly consisting of hepatocellular carcinoma (HCC), is one of common malignancies worldwide, and prevalent among the Chinese population. A diagnosis of early stage HCC has proven to be very difficult because of its insidious feature in onset and development. At the time of diagnosis, most HCC cases are locally advanced and/or distant metastatic, which results in difficulty to be treated and poor prognosis. For advanced HCC, systemic therapy is frequently adopted as an important palliative method. In recent years, clinical studies and observations have often reported about systemic anti-cancer therapy of advanced HCC, including molecular target therapy, systemic chemotherapy and immunotherapy. In this article, we review these treatment modalities to provide a reference for clinicians.

Key words: Hepatocellular carcinoma; Systemic therapy; Molecular targeted therapy; Chemotherapy; Progress

Core tip: This review describes the progress in systemic therapy of advanced hepatocellular carcinoma (HCC) in recent years from several aspects. First, we describe the progress in molecular targeted therapy of HCC. Second, we highlight systemic chemotherapy especially oxaliplatin-based regimens. Third, we introduce some new information of immunotherapy and arginine deprivation therapy. At the end of the article, we have a brief summary and discuss the future direction of development.

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INTRODUCTION

Primary liver cancer (PLC) is one of the most common malignant tumors in the world. Hepatocellular carcinoma (HCC) accounts for about 90% of PLC cases. Its incidence rate is rising around the world. According to the statistics from the latest global cancer survey by the World Health Organization (WHO)[1], there were 782500 newly diagnosed cases and more than 700000 HCC-related deaths in 2012, making HCC the second most common cause of cancer-related deaths worldwide. The numbers of new cases and mortalities of HCC from China account for above 50% of the global annual data. Additionally, the incidence and mortality rates, respectively, rank third and second among all malignancies in China[2,3]. Although the mortalities from many malignancies are gradually declining in the United States, the HCC mortality rate is still rising[4].

Because of its insidious onset, aggressive invasion, rapid progression and difficulty of early diagnosis, most HCC cases are locally advanced or metastatic at the time of diagnosis, unsuitable for local regional therapies including surgical excision, liver transplantation, local ablation and transcatheter arterial chemoembolization (TACE). These cases are generally classified as the advanced HCC, including Barcelona Clinic Liver Cancer (BCLC) stages C and D with very poor prognosis. Even with the best supportive care (BSC) for these patients, the survival period averages from 6 to 9 mo in European and American patients and only 3 to 4 mo in Asian patients (excluding Japan). Although sorafenib, a molecular targeted drug, has been approved for the treatment of advanced HCC, its application in the clinic is greatly limited because of low response rate (RR), limited survival benefit, toxicity and very high price. Furthermore, no drugs are currently available if there is resistance to sorafenib. There is an urgent need to actively seek new choice and breakthrough in systemic treatment of advanced HCC. In recent years, the hotspots in liver cancer field are translational and clinical studies of treatment of advanced HCC. For example, new targeted drugs, acting on key points in HCC occurrence and development, such as c-MET inhibitors, are in clinical trials now. Progress has also been made in systemic chemotherapy, especially with the EACH study[5,6]. This study has shown that the oxaliplatin (OXA)-based regimens were able to provide definite survival benefit for advanced HCC patients from Asia, especially China. Moreover, immune checkpoint inhibitors, a hot research topic, have shown promising effects in the treatment of advanced HCC in preliminary trials. This review will discuss new research and prospects for future development of treatments for HCC.

MOLECULAR TARGET DRUGS

Sorafenib, with trade name Nexavar, is an oral multi-targeted tyrosine kinase inhibitor with dual antitumor effects. On one hand, sorafenib can directly inhibit the growth of tumor cells by interfering with the RAF/MEK/ERK signaling pathway. On the other hand, it can block tumor angiogenesis process by suppressing vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR). Two large, randomized, placebo-controlled, international multicenter clinical trials, SHARP[7] and Oriental[8], have shown that sorafenib can delay tumor progression and prolong survival of patients with advanced HCC. Thus, sorafenib has already been approved in more than 180 countries and regions for the treatment of inoperable or metastatic HCC. A series of clinical studies on new targeted agents for HCC treatment have been conducted (Table 1), including the first-line or second-line treatment, and monotherapy or combination therapy. These agents include multi-targeted drugs similar to sorafenib (such as brivanib[9,10], sunitinib[11] and linifanib[12]), ramucirumab[13] (an anti-VEGFR-2 monoclonal antibody), everolimus[14] (an mTOR inhibitor) and erlotinib[15] (an EGFR inhibitor). Unfortunately, all these studies totally failed. So far, sorafenib is still the standard treatment for advanced HCC. If patients with advanced HCC are refractory to sorafenib, there are no other standard treatments available. Therefore, advanced HCC treatment has proven to be extremely complicated and difficult. Numerous experiences demonstrate that individualized therapy should be pursued. The etiology, race, area and background liver diseases (including hepatitis, cirrhosis and impaired liver function), clinical manifestation, treatment strategy and prognosis of patients are obviously different and should be taken into account. Especially, Asian and Western patients with HCC should be treated differently because there may be differences in molecular pathogenesis of HCC based on racial and regional differences[16]. Additionally, it is also very important to monitor and rectify adverse events, by modifying dosage, to develop valuable biomarkers and improve study level. For instance, in the phase Ⅲ trial of ramucirumab acting as the second-line therapy, investigators found that ramucirumab may improve the survival of patients with AFP > 400 μg/L at baseline. In order to prove this finding, a new phase Ⅲ trial REACH-2 was designed[17]. The study has begun to recruit 399 patients. Recently some novel molecular targeted drugs and new trial design for the treatment of advanced HCC are actively ongoing. Some of them have been considered as promising candidates.

Regorafenib

Regorafenib, a sorafenib derivative, is an oral multi-targeted inhibitor with activity against multiple kinases including VEGFR1-3, TIE2, c-kit, Ret, wild type or V600-mutated B-RAF, PDGFR and fibroblast growth factor receptor (FGFR). A pilot phase Ⅰ trial[18] has preliminarily proved its safety and recommended a

Table 1 Completed randomized phase Ⅲ clinical trials of targeted drugs in hepatocellular carcinoma (2013-2015)

Drug studied	Main targets	Treatment line	Patients	RR/DCR	TTP (mo)	OS (mo)
Brivanib *vs* sorafenib (BRISK-FL, NCT00858871)	VEGFR2, FGFR1	1st	Brivanib (n = 577) Sorafenib (n = 578)	12% *vs* 9%, P = 0.0569 66% *vs* 65%, P = 0.8739	4.1 *vs* 4.2; HR = 1.01 (95%CI: 0.88-1.16); P = 0.8	9.5 *vs* 9.9; HR = 1.05 (95%CI: 0.94-1.23); P = 0.31
Brivanib *vs* placebo (BRISK-PS, NCT01108705)		2nd	Brivanib (n = 263) Placebo (n = 132)	10% *vs* 2%, P = 0.003 61% *vs* 40%, P < 0.001	4.2 *vs* 2.7; HR = 0.56 (95%CI: 0.42-0.78); P = 0.001	9.4 *vs* 8.2; HR = 0.89 (95%CI: 0.69-1.15); P = 0.33
Sunitinib *vs* sorafenib (SUN, NCT00247676)	VEGFR, PDGFR, c-KIT, RET	1st	Sunitinib (n = 530) Sorafenib (n = 544)	< 7.2% *vs* < 6.9%, P = NR 50.8% *vs* 51.5%, P = 0.816	3.8 *vs* 4.1; HR = 1.13 (95%CI: 0.98-1.31); P = 0.16	7.9 *vs* 10.2; HR = 1.30 (95%CI: 1.13-1.5); P = 0.001
Ramucirumab *vs* placebo (REACH, NCT01140347)	VEGFR	2nd	Ramucirumab (n = 283) Placebo (n = 282)	7.1% *vs* < 0.7%, NR	3.5 *vs* 2.6; HR = 0.59 (95%CI: 0.49-0.72); P = 0.0001	9.2 *vs* 7.6; HR = 0.866 (95%CI: 0.72-1.05); P = 0.14
Everolimus *vs* placebo (EVOLVE-1, NCT01035229)	mTOR	2nd	Everolimus (n = 362) Placebo (n = 184)	2.2% *vs* 1.6%, P = NR 56.1% *vs* 45.1%, P = 0.01	3.0 *vs* 2.6; HR = 0.93 (95%CI: 0.75-1.15); P = NA	7.6 *vs* 7.3; HR = 1.05 (95%CI: 0.86-1.27); P = 0.67
Linifanib *vs* sorafenib (LIGHT, NCT01009593)	VEGFR, PDGFR	1st	Linifanib (n = 517) Sorafenib (n = 518)	13% *vs* 6.9%, P < 0.001 NR	5.4 *vs* 4.0; HR = 0.76 (95%CI: 0.64-0.89); P < 0.001	9.1 *vs* 9.8; HR = 1.04 (95%CI: 0.89-1.22); P = NS
Sorafenib + erlotinib *vs* sorafenib + placebo (SEARCH, NCT00901901)	EGFR	1st	Sorafenib + erlotinib (n = 362); Sorafenib + placebo (n = 358)	7% *vs* 4%, P = 0.051 44% *vs* 53%, P = 0.0104	3.2 *vs* 4.0; HR = 1.13 (95%CI: 0.94-1.36); P = 0.91	9.5 *vs* 8.5; HR = 0.92 (95%CI: 0.78-1.1); P = 0.2

CI: Confidence interval; EGFR: Epidermal growth factor receptor; DCR: Disease control rate; FGFR: Fibroblast growth factor receptor; HR: Hazard ratio; NA: Not applicable; NR: Not reported; NS: Not significant; OS: Overall survival; PDGFR: Platelet-derived growth factor receptor; PFS: Progression-free survival; RR: Response rate; TTP: Time to progression; VEGFR: Vascular endothelial growth factor receptor.

therapy that consists of 160 mg/d for 21 d and a 7-d break. A multicenter, open-label, phase Ⅱ study[19] has assessed the safety and efficacy of regorafenib in 36 patients with advanced HCC who resisted sorafenib treatment. The results have shown that disease control was achieved in 26 patients, of whom one had a partial response (PR) and the others had stable disease (SD). Median time to progression (mTTP) and median overall survival (mOS) were 4.3 mo and 13.8 mo, respectively. Regorafenib showed an acceptable safety profile. The most frequent drug-related adverse events were fatigue (17% of patients), hand-foot skin reaction (14%) and diarrhoea (6%). On this basis, a phase Ⅲ study (RESORCE, NCT01774344) has been conducted to assess the efficacy and safety of regorafenib in advanced HCC patients. The study intends to enroll 530 patients with overall survival (OS) as its primary endpoint. On May 4, 2016, Bayer announced that RESOURSE study met its primary endpoint of a statistically valid improvement in OS. Detailed efficacy and safety analyses from this study are expected to be presented at an upcoming scientific congress. Regorafenib is the second successful molecular targeted drug after sorafenib, which has an epoch-making significance for the treatment of HCC.

Lenvatinib

Lenvatinib is also a novel tyrosine kinase inhibitor with multiple targets including VEGFR, FGFR, PDGFR, RET and KIT. A phase Ⅰ clinical trial has shown that lenvatinib had a favorable safety and tolerability profile with evidence of antitumor activity on HCC[20,21]. The study recommended that during the further phase Ⅱ clinical trial lenvatinib would be administered at 12 and 8 mg once daily in HCC patients with Child-Pugh A (5-6 score) and Child-Pugh B (7-8 score) liver function, respectively. A multicenter, open-label, phase Ⅰ/Ⅱ study of lenvatinib (E7080-J081-202) has been conducted in Japan and South Korea, and 46 patients were enrolled. The results have demonstrated that RR and SD were 37% and 45.7%, respectively, with mTTP of 12.8 mo and mOS of 18.7 mo. The most common adverse events were hypertension (76% of patients; Grade 3, 54%), hand-foot syndrome (61%; 7%), proteinuria (59%; 20%), anorexia (57%; 2%), thrombocytopenia (50%; 33%) and fatigue (48%; 0%). Based on the above results, a multicenter, randomized, open-label, phase Ⅲ clinical trial, aiming to compare the safety and effectiveness between lenvatinib and sorafenib for the treatment of advanced HCC patients only with Child-Pugh class A liver function, is under way, with completion of patient recruitment[22].

Apatinib

Apatinib is a novel oral multi-kinase inhibitor of VEGFR-2. Based on the result of a randomized, double-blind, placebo-controlled phase Ⅲ trial[23] in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction, apatinib has been approved in China for the treatment of chemotherapy-refractory advanced or metastatic gastric cancer. We reported a multicenter, randomized, open-label, dose-finding, phase Ⅱ trial

of apatinib as first- line treatment in Chinese patients with advanced HCC[24]. Treatment naive patients with advanced HCC had Child-Pugh class A liver function were randomized to receive apatinib 850 mg/q.d. or 750 mg/q.d. A total of 121 patients were enrolled. For efficacy, mTTP of the 850 mg group and the 750 mg group was 4.2 mo and 3.3 mo, respectively, and mOS was 9.7 mo and 9.8 mo, respectively. Apatinib has been well tolerable in patients. Most of the adverse event could be managed by dose interruptions or reductions. There was no significant favorable safety profile between two groups; above 2% of patients developed elevated aminotransferase, thrombocytopenia, elevated bilirubin, hypertension, leukocytopenia, hand-foot syndrome or fatigue. Results of this uncontrolled phase Ⅱ study indicated that apatinib has potential survival benefit in patients with advance HCC. A multicenter, randomized, double blind, phase Ⅲ trial (NCT02329860) is ongoing to evaluate the efficacy and safety of apatinib in patients with advanced liver cancer who have progressed on systemic therapy (chemotherapy and/or targeted therapy). Approximately 360 patients who meet the entry criteria will be randomly assigned at a 2:1 ratio to receive apatinib or placebo (1/3 chance to receive placebo). Primary endpoint of the study is OS.

MEK inhibitors

Refametinib is an oral MEK inhibitor. Treatment combination of refametinib and sorafenib can induce a definite survival benefit in advanced HCC patients[25]. Among these patients, RR and disease control rate (DCR) were 6.2% and 43%, respectively. mTTP and mOS were 122 and 290 d, respectively. Furthermore, the best clinical response was observed in subgroup with RAS mutations. This combination therapy, however, showed an obvious toxicity profile. The incidence rate of grades 3 and 4 adverse events was as high as about 80%. Four patients died from adverse events (liver function failure, hepatic encephalopathy, tumor lysis syndrome and unknown reason for one case). Most frequent drug-related adverse events were rash, gastrointestinal tract reaction (nausea, vomiting and anorexia) and elevated transaminase. Almost all of subjects who suffered from adverse events had to undergo dose modifications. A phase Ⅱ study is currently underway to explore the efficacy of refametinib monotherapy in advanced RAS-mutated HCC.

C-MET inhibitors

Proto-oncogene c-MET can encode the hepatocyte growth factor (HGF) receptor. The binding of HGF to its receptor is able to initiate downstream signaling pathways and then produce oncogenic responses. This mechanism may play a key role in the development of HCC. Both expression and transcription of c-MET were increased in HCC samples. c-MET overexpression is also related with vascular invasion, tumor recurrence, and short survival period. Therefore, c-MET may be a potential therapeutic target for the treatment of HCC[26,27].

Tivantinib

Tivantinib (ARQ 197) is the most investigated selective c-MET inhibitor in oral form. Similar to vincristine, it induces disruption of microtubules to exert an antitumor effect[28]. A phase Ib study has investigated the safety profile on 20 patients whose liver function was scored as Child-Pugh A or B[29]. The results were encouraging. The most frequent non-hematologic toxicities included fatigue (55%), alopecia (15%), anorexia and diarrhea (15%). The grade 3/4 hematologic toxicities included neutropenia (38%) and anemia (24%). Thus, careful surveillance of hematologic toxicity is needed during the treatment period. A dose of 360 mg BID was recommended in a subsequent phase Ⅱ study. A multicenter, randomized, placebo-controlled phase Ⅱ clinical trial was conducted on patients with advanced HCC and Child-Pugh A cirrhosis[30,31]. Those patients had progressed on or were unable to tolerate first-line systemic therapy (the treatment modality was sorafenib except for four cases receiving sunitinib). In this study, researchers randomly allocated patients at a ratio of 2:1 to receive tivantinib (360 mg BID) or placebo. The primary endpoint was TTP, and the secondary endpoints were progression free survival (PFS), OS and RR. Because of high incidence of severe neutropenia after recruitment of 57 patients (38 patients in the treatment group), the tivantinib dose was amended to 240 mg twice-daily. Seventy-one patients had received tivantinib treatment (38 at 360 mg twice-daily and 33 at 240 mg twice-daily), and 36 patients were randomly assigned to receive placebo. The result has shown that mTTP was longer for patients treated with tivantinib than that for placebo (1.6 mo *vs* 1.4 mo, HR: 0.64, 90%CI: 0.43-0.94, $P = 0.04$). For patients with MET-high tumors ((high expression was regarded as $\geqslant$ 2+ in $\geqslant$ 50% of tumor cells), tivantinib was able to prolong mTTP (2.7 mo *vs* 1.4 mo, HR: 0.43, 95%CI: 0.19-0.97, $P = 0.03$) and mOS (7.2 mo *vs* 3.8 mo, HR: 0.38,95%CI: 0.18-0.81, $P = 0.01$) in comparison with placebo, and was able to increase DCR (50% *vs* 20%). For patients with MET-low tumors, there were no differences in mTTP, mOS or DCR. The dose of 240 mg BID was tolerable in toxicity. The grade 3 hematologic adverse events included anemia (9%), neutropenia (6%) and thrombocytopenia (6%). The study recommended tivantinib at a dosage of 240 mg BID as an option for second-line treatment of patients with advanced HCC.

A placebo-controlled phase Ⅲ clinical trial is ongoing to assess the efficacy and safety of tivantinib for second-line treatment of c-MET positive HCC (NCT01755767; Study of tivantinib in subjects with inoperable HCC who have been treated with one prior therapy). The result is well expected.

Cabozantinib

Cabozantinib is an oral agent with anti-tumor effects through targeted inhibition of MET, VEGFR-2 and RET signaling pathways. Based on the favorable results of a phase Ⅲ study[32], cabozantinib has been approved by the FDA for the treatment of advanced medullary thyroid carcinoma. A phase Ⅱ clinical trial[33] has been performed to explore the efficacy of cabozantinib on HCC patients whose previous systemic therapies were failed. The obtained results were satisfactory: the mPFS was 4.2 mo, of which 5% of patients (2/36) were confirmed to achive PR. DCR at 12 wk was 68%; AFP level of 38% (10/26) patients with an abnormal AFP level at baseline was decreased by > 50%. The most common adverse events were diarrhea (17%), hand-foot syndrome (15%) and thrombocytopenia (10%). A phase Ⅲ trial is ongoing to compare the efficacy of cabozantinib *vs* placebo as the second-line treatment for advanced HCC patients (NCT01908426; study of cabozantinib (XL184) *vs* placebo in subjects with HCC who have received prior sorafenib, CELESTIAL).

Other c-MET inhibitors

Foretinib is a multi-kinase inhibitor targeting MET, RON, AXL, TIE-2 and VEGFR. A phase Ⅰ/Ⅱ study has enrolled 39 patients who have not received sorafenib or other tyrosine kinase inhibitors previously[34]. The dose of foretinib was 30 mg/d. The results have shown that RR was 24%, DCR was 79%, and the mTTP was 4.2 mo. Foretinib proved to have a high safety profile and was well tolerated. The most common adverse events were hypertension, fever and loss of appetite. Tepotinib (MSC2156119J) is a highly selective c-MET inhibitor with favorable safety and promising antitumor activity, particularly in c-Met positive tumors. Tepotinib is well tolerated and active in Asian patients with advanced HCC in a phase Ib/Ⅱ trial[35]. The ongoing phase Ⅱ part of this study is comparing the efficacy and safety of first-line tepotinib and sorafenib in patients with c-MET positive HCC. Capmatinib (INC280)[36] is a potent, selective c-MET inhibitor that causes regression of c-MET dysregulated animal solid tumor models at well-tolerated doses. An open-label, single-arm study is evaluating the safety and efficacy of INC280 in patients with c-MET positive advanced HCC, who have received no prior systemic therapy (NCT01737827). Preliminary results showed that oral INC280 600 mg BID was well tolerated with a manageable safety profile, and showed activity in patients with high c-MET status HCC[37]. In addition, there are some small molecule c-MET inhibitors, such as LY2875358[38], golvantinib[39] and emibetuzumab[40], all of which have been under study.

TGF-β inhibitor

Transforming growth factor beta (TGF-β) is closely related to the occurrence and development of HCC. Inhibiting this signal transduction pathway may effect on the control of the HCC development. As a TGF-receptor kinase inhibitor, LY2157299 is able to block TGF-β signaling transduction highly selectively. In a phase Ⅱ study[41], 109 patients with advanced HCC, who progressed on or were unable to tolerate sorafenib therapy, were randomized to receive 160 mg/d (group A, 37 cases) or 300 mg/d (group B, 72 cases) treatment. mTTP and mOS of all patients were 12 and 36 wk, respectively. For patients with AFP changes (the AFP level was decreased in 24% of patients by > 20% compared to baseline), the mOS was 93.1 wk. But the mOS of patients without AFP change was only 29.6 wk. Only four patients withdrew because of adverse reactions related to drug. The most common grade 3 or 4 adverse reactions were neutropenia (3 cases), weakness (2 cases) and anemia (3 cases). A dose of 300 mg/d was recommended for subsequent studies. A study using LY2157299 combined with sorafenib is being carried out.

Other targeted drugs

Pazopanib is a multi-kinase angiogenesis inhibitor targeting VEGFR1-3, PDGFR-α, β and c-Kit. A phase Ⅰ dose-finding study[42] showed that pazopanib had a manageable safety profile in patients with advanced HCC, and 600 mg was chosen for further research. Moreover, pazopanib reduced tumor vessel leakage, as shown by dynamic contrast-enhanced magnetic resonance imaging, indicating a direct effect on HCC vasculature that might be associated with its antitumor activity.

Axitinib is a potent and selective inhibitor of VEGFRs 1-3, approved as second-line therapy for advanced renal cell carcinoma. McNamara[43] reported promising clinical activity of axitinib as second-line therapy for HCC in a single-arm, open-label phase Ⅱ study. The study met its primary endpoint with a tumor control rate of 42.3% at 16 wk (> 20%). In a randomized phase Ⅱ study of axitinib *vs* placebo plus BSC in second-line treatment of advanced HCC[44], patients in the axitinib arm achieved longer PFS (P = 0.004) and TTP (P = 0.006), and higher CBR (P = 0.003) compared with those in the placebo arm. However, axitinib did not improve OS over placebo in the overall population or in stratified subgroups. The toxicities were acceptable.

SYSTEMIC CHEMOTHERAPY

For patients with advanced HCC, systemic chemotherapy was used clinically as a palliative method. Before publication of the EACH study, there were no standard drugs or regimen that can be regarded as the golden standard. There was also a lack of high-level, evidence-based studies showing that systemic chemotherapy had achieved survival benefit. During the past two decades, several high efficiency drugs with low

toxicity, such as OXA, have been developed and used clinically. Additionally, with the optimization of clinical trials and the achievements from trials, the traditional concept that HCC is unsuitable for chemotherapy has been questioned or challenged. Many researchers have actively investigated the effects of OXA alone or combined with other drugs (including chemotherapeutic and molecular targeted drugs) on advanced HCC. A series of clinical trials have obtained promising results that have gradually confirmed the efficacy of OXA for treatment of advanced HCC.

FOLFOX 4 regimen

We have conducted an open, multicenter randomized controlled phase Ⅲ clinical trial for the treatment of advanced HCC patients who were unsuitable for surgery or local treatment (EACH study)[5,6]. The study recruited 371 patients, with Chinese patients accounting for 75% (70% from China mainland and 5% from Taiwan), and the remaining patients from South Korea (14%) and Thailand (11%). Patients were randomly divided into two groups to receive either FOLFOX 4 treatment or doxorubicin alone. The treatment continued until disease progression, unacceptable toxicity, death occurred or the original lesion became suitable for surgery. Hierarchical factors included different countries and regions, disease state and BCLC stage. The primary endpoint was OS, and secondary endpoints included PFS, RR, DCR and safety. Baseline characteristic of both groups were uniform and comparable. The results showed that compared with doxorubicin, FOLFOX4 treatment prolonged mPFS significantly (1.77 mo *vs* 2.93 mo, $P < 0.001$); RR were 67% and 8.15% ($P = 0.02$), respectively; DCR were 31.55% and 52.17% ($P < 0.0001$), respectively; mOS trended towards improvement (6.40 mo *vs* 4.97 mo, $P = 0.0695$). The further follow-up of 7 mo showed that mOS in the FOLFOX4 group was beneficial (6.47 mo *vs* 4.90 mo, $P = 0.04$). In the main target population, namely, the Chinese patient population, mOS was significantly prolonged in the FOLFOX4 group in comparison with the doxorubicin group (5.9 mo *vs* 4.3 mo, $P = 0.0281$); in terms of mPFS, RR and DCR, FOLFOX4 treatment showed a significant advantage (2.4 mo *vs* 1.7 mo, 8.6% *vs* 1.4% and 44.0% *vs* 30.8%). OS and PFS benefits were also consistent in all subgroups. In terms of toxicity, the incidence of neutropenia and neurotoxicity in the FOLFOX4 group was mildly higher than that in the control group. But there were no differences in the incidence of grade 3/4 adverse reactions between the two groups, which were similar to those observed in other studies using FOLFOX4 in colorectal cancer. No new toxicity events were reported. FOLFOX4 is convenient, well tolerated and safe.

The EACH study was required by clinical practice and current status of HCC in China. Because of the commonly used drug doxorubicin acting as a positive control, the EACH study was significantly different from two other phase Ⅲ trials of sorafenib (both using placebo as a control) and was more in line with the requirements of clinical practice and medical ethics. Both the primary endpoint (OS) and secondary endpoints were improved in the EACH study. Most importantly, for Chinese patients who accounted for 75% of all cases, the results of Chinese subgroup have shown that all endpoints were reached. Therefore, this study was the first to demonstrate that OXA-based FOLFOX4 regimen was safe and could yield survival benefit for patients. Meanwhile, this study not only challenged and subverted the traditional concept that the systemic chemotherapy for HCC was ineffective, but also set the standard of systemic chemotherapy treatment for advanced HCC. On March 12, 2013, Chinese Food and Drug Administration (CFDA) formally approved the OXA-containing FOLFOX4 regimen for treatment of advanced HCC. Therefore, OXA became the first cytotoxic drug that was officially approved by the governmental drug administration for HCC chemotherapy worldwide.

GEMOX regimen

In Western countries, the GEMOX regimen (gemcitabine combined with OXA) has been commonly used in the treatment of HCC. Zaanan *et al*[45] reported a large, multicenter, retrospective study, which used GEMOX to treat advanced HCC. A total of 204 consecutive patients with advanced HCC were included in this study (median age 60 years; men, 86%; underlying cirrhosis, 76%). The overall RR and DCR were 22% and 66%, respectively. mPFS, mTTP and mOS were 4.5, 8.0 and 11.0 mo, separately. Notably, 8.5% of patients had become eligible for curative-intent therapies because of downstaging, and 5 patients received two stage radical resections. Additionally, cirrhosis, CLIP score (Cancer of the Liver Italian Program, the Italy prognostic scoring system) and response to GEMOX were found to be independently associated with OS. Some researchers attempted to use the GEMOX as a second-line method. Patrikidou *et al*[46] performed a multicenter retrospective analysis of 40 advanced HCC patients that received average 7 cycles of GEMOX chemotherapy after at least one series of anti-angiogenic therapy, including sorafenib, sunitinib, bevacizumab and brivanib). Grade 3 or 4 toxicity was observed in 25% of patients, mainly neurotoxicity, thrombocytopenia and neutropenia in 12.5%, 5 % and 5% of patients, respectively. Grade < 3 toxicity was mainly hematological and neurotoxicity. In 35 patients evaluable for response, PR was observed in 20% of patients, while 46% had SD. mOS was 8.3 mo, with a 6-mo OS rate of 59%. mPFS was 3.1 mo. Such factors as performance status, AFP levels at the beginning of GEMOX treatment and BCLC score at the time of diagnosis were associated with OS independently.

META-ANALYSIS

Petrelli *et al*[47] have conducted a meta-analysis to

quantify the benefits of OXA-based chemotherapy in advanced HCC patients, which had not been exposed to sorafenib. Using PubMed, Web of Science, SCOPUS, the Cochrane Register of Controlled Trials and EMBASE, they selected these studies that met the following criterions: (1) prospective or retrospective clinical studies; (2) case number equal to or more than 10; (3) patients did not receive sorafenib for advanced HCC; (4) patients received OXA-based chemotherapy; (5) published in English; (6) RR data; and (7) including at least PFS or OS in results. Phase I clinical studies, second-line treatment and combined TACE studies were not included. Thirteen studies, including the Phase Ⅲ study (EACH study), were included in this review, with a total of 800 patients. In addition to OXA, the combined drugs included gemcitabine (6 studies), 5-flurouracil (5-Fu) or capecitabine (6 studies) and doxorubicin (1 study). Four studies had also added bevacizumab (Avastin) or cetuximab. The RR was 16.8% (95%CI: 12.8%-21.6%) in all studies, 20% in the GEMOX regimen and 15% in the combined capecitabine regimen, and was related with the one-year survival rate. The median PFS and OS were 4.2 and 9.3 mo, respectively, with one-year PFS rate of 18% and one-year survival rate of 37%. The weighted mPFS, mOS and RR were 4.5, 11 mo and 20% in Western patients, respectively. Conversely, in Asian studies, the mPFS, mOS and RR were 2.43, 6.47 mo and 13.2%, respectively. The mPFS and mOS were 3.3/6.47 mo in capecitabine-based studies, and were 4/11 mo in OXA-based studies. Therefore, OXA-based chemotherapy is effective and represents a viable option in advanced HCC patients. Meanwhile, their findings also confirmed that outcome of liver cancer treatment was obviously different between Eastern and Western patients, and Eastern patients had a worse outcome.

Liu *et al*[48] also reported another meta-analysis. Besides the above-mentioned databases, the authors searched Chinese databases as well, such as China Academic Journal Full-text Database (CNKI), Chinese biological medical literature database (CBM) and Wanfang database (CECDB). It included prospective studies, randomized controlled clinical ones and cohort ones, and studies with more than 30 cases. Finally, 12 studies, in which two were randomized controlled ones, were included in this meta-analysis, with a total of 600 advanced HCC patients. The results showed that RR, mPFS and mOS were 14%, 4.7 and 9.5 mo, respectively. One-year PFS rate and one-year survival rate were 19% and 35.6%, respectively. Moderate and severe adverse reactions were neutropenia (16.6%), thrombocytopenia (8.7%), anemia (5.4%), neurotoxicity (4.9%), nausea/vomiting (1.8%) and diarrhea (2.9%). Subgroup analysis showed that RR of Asian and Western patients were 13.9% (95%CI: 8.1%-19.7%) and 14.2% (95%CI: 5.3%-23.1%), respectively. In Asian patients, mPFS and mOS were 3.0 and 9.4 mo, respectively, and one-year PFS rate and one-year survival rate were 12.9% and 30.3%, respectively. In Western patients, mPFS and mOS were 4.7 and 9.5 mo, respectively, and one-year PFS rate and one-year survival rate were 20.0% and 42.4%, respectively.

The above two meta-analyses also have some limitations. Except for the EACH study, all studies were single arm ones without a control group and with small sample size. The best combination of drugs was not identified. In Petrelli's report, GEMOX regimen seemed to be better. Due to a lack of detailed information and data of patients, prognostic factors that are related to remission and clinical benefit could not be evaluated.

SYSTEMIC CHEMOTHERAPY COMBINED WITH SORAFENIB

Doxorubicin has traditionally been used in clinical practice for treatment of HCC. Several previous studies have shown that doxorubicin had limited antitumor efficacy, but was not confirmed in large sample trials. A randomized phase Ⅱ study reported by Abou-Alfa[49] comparing doxorubicin alone to doxorubicin plus sorafenib, showed a significant improvement in OS from combination therapy. Based on these results, CALGB80802 study[50] was designed to determine whether doxorubicin plus sorafenib could improve survival compared to sorafenib alone. Patients with histologically proven advanced HCC, no prior systemic therapy and Child-Pugh A liver function were randomized to receive doxorubicin 60 mg/m^2 per 21 d plus sorafenib 400 mg p.o. twice daily or sorafenib alone. The primary endpoint was OS and secondary endpoint was PFS. The study planned to include 480 patients, but was halted after accrual of 346 patients. A planned interim analysis showed that the addition of doxorubicin to sorafenib resulted in higher toxicity and did not improve OS or PFS. mOS was 9.3 mo (95%CI: 7.1-12.9) for doxorubicin plus sorafenib, and 10.5 mo (95%CI: 7.4-14.3) for sorafenib with a hazard ratio (HR) of 1.06 (95%CI: 0.8-1.4). mPFS was 3.6 (95%CI: 2.8-4.6) and 3.2 mo (95%CI: 2.3-4.1), respectively (HR = 0.90, 95%CI: 0.72-1.2). An important reason for the failure of this trial may be the change of the control group: doxorubicin in phase Ⅱ study but sorafenib in phase Ⅲ study.

Williet *et al*[51] reported an advanced HCC case with abdominal lymph node metastasis that received the combination treatment of GEMOX regimen and sorafenib. After treatment, PR was achieved and serum AFP dropped to normal. Subsequently the patient underwent radical surgery. In a randomized, controlled, phase Ⅱ clinical study (GOTEXT study), Assenat *et al*[52] compared the efficacy of GEMOX combined with sorafenib and sorafenib alone as first-line therapy for patients with advanced HCC. A total of 94 patients were included and divided randomly into the sorafenib monotherapy (group A) and GEMOX plus

sorafenib (group B) groups. Baseline characteristics in the two groups were comparable. Median treatment time and dose intensity in group A were accordant, while median cycle number of GEMOX regimen in group B was 7 (1-12). Results have shown that RR and DCR of the two groups were 9% *vs* 70%, and 16% *vs* 77%, respectively; after a median follow-up of 17.6 mo, 4-mo PFS rates of two groups were 54% and 61%, respectively, and mOS was 13 and 13.5 mo, respectively. The main adverse reactions of the two groups were neutropenia, diarrhea, fatigue, thrombocytopenia, peripheral neuropathy and hand-foot syndrome. The authors believed the primary endpoint of their study was reached (4-mo PFS rate greater than 50%), and mPFS and mOS were favorable. So the combination of sorafenib and GEMOX regimen is suitable for HCC treatment. Yau *et al*[53] reported a multicenter phase Ⅱ clinical study conducted by Hong Kong and Singapore Liver Cancer Collaborative Group. Fifty-one patients, of whom 84% had HBV infection, 90% had BCLC stage C and 80% had extrahepatic metastasis, were enrolled in their study. All patients received SECOX regimen (sorafenib, 400 mg BID. days 1-14; OXA, 85 mg/m^2 day 1 and Cap 1700 mg/m^2 days 1-7 in 2-wk cycles). The primary endpoint was TTP, and second endpoints were RR, PFS, OS and tolerance. The results have shown that RR was achieved in 16% of patients, SD (lasted at least 8 wk) achieved in 62%, and mTTP, mPFS and mOS were 5.29 mo, 5.26 mo and 11.73 mo, respectively. The most common grades 1-2 adverse events were diarrhea (75%), hand-foot skin reaction (73%) and liver function abnormality. No treatment related deaths occurred. The study has demonstrated that SECOX regimen was of better efficacy and safety for Asian HCC patients.

Thus, the combination of OXA-based systemic chemotherapy and sorafenib has a potential synergistic effect with favorable results from phase Ⅱ studies. It not only improved RR, but also prolonged TTP, PFS and OS. It is worth being further studied through larger sample-sized randomized clinical trials.

IMMUNOTHERAPY

In recent years with new findings on tumor immune escape and immune tolerance mechanisms, tumor immunotherapy has developed rapidly. Especially, immune checkpoint inhibitors, such as ipilimumab (anti-CTLA-4 antibody)[54], pembrolizumab (anti-PD 1 monoclonal antibody)[55] and nivolumab (anti-PD 1 monoclonal antibody)[56,57], have proven successful in the treatment of malignant melanoma tumor, non-small cell lung cancer and renal cell carcinoma. Tumor immunotherapy was named the 2013 best scientific breakthrough by several top academic magazines. The magazine Science said: "This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off!" This is a great inspiration to HCC research.

Tremelimumab

One transmembrane receptor on T cells, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4, also known as CD152), is a kind of white blood cell differentiation antigen. After binding with its molecular ligand B7, CTLA-4 can inhibit T cell activation, thus protecting tumor cells from T cell attack. Blocking the immune effect of CTLA-4 can stimulate immune cell proliferation, and induce or enhance an antitumor immune response[58].

Tremelimumab (CP657 206) is a humanized anti CTLA-4 IgG2 antibody with a long half-life (22 d)[59]. In an exploratory study, the application of tremelimumab achieved impressive results for the treatment of 21 HCC patients with chronic hepatitis C virus (HCV) infection. RR and DCR were 18% and 76%, respectively, and mTTP was 6.48 mo. Tremelimumab was also observed to induce a significant drop in viral load with antiviral activity[60]. TACE and radiofrequency ablation (RFA) are the common local therapies for HCC treatment, both of which can induce immune reaction against HCC and then strengthen the efficacy of the anti-CTLA-4 treatment. At the 2015 American Society of Clinical Oncology (ASCO) annual meeting, a researcher reported a study about efficacy of combined tremelimumab and TACE or RFA on HCC[61]. A total of 20 patients were enrolled in this study, of whom 18 completed assessments. The most common adverse reactions were itching, with only 1 patient withdrawing due to pneumonia; his DFS was 16 mo. Of 10 patients treated with TACE/RFA, 4 (40%) achieved PR. Of 7 patients with HCV infection, 5 were observed to have a significant drop in viral load. The results of the tumor biopsy, which was performed at 6 mo, showed immune cell infiltration in tumor tissues of all patients. mPFS was 7.4 mo. The study has shown that tremelimumab combined with TACE or RFA is safe and feasible for the treatment of advanced HCC. This regimen could also reduce viral load in patients with HCV infection. mTTP and RR at 7.4 mo were favorable. This regimen is worth further exploration.

Nivolumab

Programmed death receptor 1, also known as PD-1, is an important immunosuppressive molecule that is produced by activated CD28$^+$ and CD4$^+$ T lymphocytes, B cells and NK cells. It was also found to be expressed on surface of regulatory T cells (Treg)/myeloid-derived suppressor cells (MDSCs)/DCs (dendritic cells)/mononuclear cells. Currently, only PD-L1 and PD-L2 are its known ligands. Many kinds of tumor cells, including HCC, can express PD-1, which is related with a poor prognosis. PD-1-PD-L1 binding can block the TCR receptor signal transduction, inhibit proliferation and secretion of cytotoxic medium of T cells, and induce depletion of T cells. This is important for tumor immune escape. Blocking the PD-1 pathway

can alleviate depletion of T cells, promoting the immune response against tumor[62].

Nivolumab is a fully humanized monoclonal IgG4 antibody against PD-1[63]. At the 2015 ASCO annual meeting, a phase Ⅰ/Ⅱ study about nivolumab in advanced HCC was reported[64]. All patients were confirmed pathologically and Child-Pugh score was less than 7. Those patients who had progressed on or were unable to tolerate or refused sorafenib therapy were recruited. According to the etiology (without hepatitis B virus infection, with hepatitis B infection or hepatitis C infection), participants were divided into three parallel cohorts and administered in a dose escalation pattern (0.1, 0.3, 1, 3, 10 mg/kg). The primary endpoint was safety. Forty-seven patients were included and their Child-Pugh score and ECOG score were 5 (n = 35) or 6 (n = 6) and 0 (n = 26) or 1 (n = 15), respectively. Of them, 71% of patients had extrahepatic metastasis and/or portal vein invasion, and 77% were treated previously with sorafenib. At the time of report, there were still 17 patients remaining in the study. Thirty patients withdrew (26 due to disease progression, and two due to drug-related adverse events) and the rest achieved complete response (CR). A total of 32 (68%) patients developed different grades of drug-related adverse events (grade 3/4 in 19% of patients), most of which were elevated aspartate aminotransferase (AST) (19%), elevated serum lipase (17%), rash (17%), and elevated alanine aminotransferase (ALT) (15%). Severe adverse events with an incidence more than 5% were elevated AST (11%), elevated ALT (9%) and elevated serum lipase (6%). Of 42 evaluable patients, two achieved CR (5%) and 8 achieved PR (18%). Their 9-mo survival rate was 70% and one-year survival rate was 62%. The preliminary results showed that nivolumab could obtain amazing outcome in term of RR and one-year survival rate. It is worthy of large sample, in-depth studies.

JX-594

JX-594 is a recombinant vaccine virus, with insertion of human granulocytemacrophage colony-stimulating factor (hGM-CSF) and β-galactosidase transgenes, and disruption of the viral thymidine kinase gene (TK) for cancer selectivity, immune stimulation and replication assessment. JX-594 is designed to induce both virus replication-dependent oncolysis and tumor-specific immunity[65].

Heo *et al*[66] and Breitbach *et al*[67] reported a dose-grouped clinical trial of JX-594 on HCC. A total of 30 patients were divided randomly into a low dose group (14 cases) and a high dose group (16 cases). Researchers injected JX-594 directly into patients' liver tumors at days 1, 15 and 29. After injection, JX-594 gene was detected in their serum. The results showed that median survival duration was significantly related to dose (median survival of 14.1 mo with high dose compared to 6.7 mo with low dose; HR = 0.39, P = 0.02). In both groups RR were 15% according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and 62% according to the Choi standard, even in distant non-injected tumors. A randomized, controlled study is ongoing to compare the efficacy of JX-594 and best supportive care for advanced HCC patients who were refractory to sorafenib. A global, randomized, open-label, phase Ⅲ study will compare the efficacy and tolerability of JX-594 followed by sorafenib *vs* sorafenib in patients with advanced HCC (PHOCUS, NCT02562755)[68].

ARGININE DEPRIVATION THERAPY

Human HCC cells are largely deficient of arginino-succinate synthetase and thus auxotrophic for arginine. Arginine deprivation can induce tumor cell death. Pegylated arginine deiminase (ADI-PEG 20) is an arginine-degrading enzyme, one of the systemic arginine deprivation agents under study. A phase Ⅰ/Ⅱ study[69] of ADI-PEG 20 showed a favorable safety profile in patients with unresectable HCC. In pretreated Asian patients with advanced HCC, ADI-PEG 20 also showed promising DCR and mOS with mild toxicities, thus deserving further exploration[70]. Based on these results, a randomized, double-blind, placebo controlled, phase Ⅲ study of ADI-PEG 20 *vs* BSC after prior systemic therapy is ongoing (NCT01287585).

CONCLUSION

HCC is one of the most common malignancies in the world, especially in China. It is very difficult to cure advanced HCC. Sorafenib brings a breakthrough for the treatment dilemma of advanced HCC. However, its effect is far from being satisfied. Besides sorafenib, many clinical studies of other new molecular targeted drugs have failed. But efforts towards exploring effective treatment regimen have continued. The pilot studies of regorafenib and lenvatinib have obtained favorable results in phase Ⅱ studies, and are waiting for confirmation by phase Ⅲ studies. Studies of C-MET inhibitors on patients whose lesions have high expression of MET are also worth highlighting. The EACH study and several meta-analyses have confirmed systemic chemotherapy, especially OXA based therapy, is safe and effective, providing a new treatment option for advanced HCC patients, especially Asian ones. Previous studies on immunotherapy, especially immune checkpoint inhibitors, have showed a surprising effect and further clinical trials with a larger sample are warranted. We can see that systemic treatment of advanced HCC has made encouraging progress.

Nevertheless, we have to remember that sorafenib, systemic chemotherapy and immunotherapy are just a part of multidisciplinary approaches for advanced HCC treatment. They are not able to cure HCC. In order to

get maximal or expected benefit, different drugs or regimens should be rationally combined together. HCC is still a big challenge and a severe health problem for China and all countries.

In the future, a variety of drugs that have been used for systemic therapy, either alone or in combination, will be involved in further large-scale clinical studies especially translational research. Meanwhile, with advanced molecular biology techniques, the possible mechanisms of drug resistance need to be investigated in depth. Additionally, since HCC is a dynamically developing disease, many factors, such as different disease status, intrahepatic metastasis or extrahepatic metastasis, performance status score, and economic condition, should be taken into account when physicians make an individualized therapy plan. Most importantly, we should integrate all therapies, including systemic chemotherapy, molecular targeted therapy, surgery, TACE, local ablation and radiotherapy, and choose the most suitable therapy, time and patient, which means implementation of individualized treatment.

More and more physicians put a high premium on systemic therapy of HCC. With the deepening of studies, improvement of treatment level, experience accumulation and optimization of treatment strategies, we look forward to getting a much better prognosis for advanced HCC.

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