**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 26208**

**Manuscript Type: TOPIC HIGHLIGHT**

**2016 Hepatocellular Carcinoma: Global view**

**Progression of systemic therapy study of advanced hepatocellular carcinoma**

Gong XL *et al*. Promising candidates for advanced hepatocellular carcinoma.

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**Author contributions:** Both authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

**Conflict-of-interest statement:** No potential conflicts of interest. No financial support.

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**Manuscript source:** Invited manuscript

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**Received:** March 30, 2016

**Peer-review started:** April 5, 2016

**First decision:** May 12, 2016

**Revised:** May 27, 2016

**Accepted:** June 28, 2016

**Article in press:**

**Published online:**

**Abstract**

Primary liver cancers, mainly consist 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 developing. At the time of diagnosis, most HCC are local 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 target therapy; Chemotherapy; study progression

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**Core tip:** This review describes the progression of systemic therapy for advanced hepatocellular carcinoma (HCC) in recent years from several aspects. Firstly, we describe the progress of molecular targeted therapy on HCC; secondly, we highlight systemic chemotherapy especially for oxaliplatin-based regimens; then 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.

Gong XL, Qin SK. Progression of systemic therapy study of advanced hepatocellular carcinoma. *World J Gastroenterol* 2016; In press

**INTRODUCTION**

Primary liver cancer (PLC) is one of the most common malignant tumors in whole world. And hepatocellular carcinoma (HCC) accounts for 90% of PLC. 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 related deaths in 2012, making HCC the second most common cause of cancer-related deaths worldwide. The new cases and mortality 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, at the time of diagnosis, most HCC reach to local advanced or distant metastatic determination of, unsuitable for local regional therapy, including surgical excision, liver plantation, local ablation and transcatheter arterial chemoembolization (TACE). These cases are generally classified as the advanced HCC, including Barcelona Clinic Liver Cancer (BCLC) stage 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. It 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 researches 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. Progression on systemic chemotherapy has also been made, 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 and especially in China. Moreover, immune checkpoint inhibitors, a hot research topic, have shown promising effect on the treatment of advanced HCC in preliminary trial results. This review will discuss new research and prospects for future treatment development for HCC.

**MOLECULAR TARGET DRUGS**

Sorafenib, with trade name Nexavar, is an oral, tyrosine kinase inhibitor of multi-targets with dual antitumor effects. Firstly, sorafenib can directly inhibit the growth of tumor cells through interfering with the RAF/MEK/ERK signaling pathway. Secondly, it can block tumor angiogenesis process through depressing 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] study 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 treatments have been conducted (shown in 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 receptor monoclonal antibody), everolimus[14] (an mTOR inhibitor) and erlotinib[15] (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 respectively 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 with ramucirumab may improve the survival of patients with AFP over 400ug/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, an 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 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 to 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 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 4th 2016, Bayer today 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 drugs after sorafenib, which has an epoch-making significance for the treatment of HCC.

***Lenvatinib***

Lenvatinib is also a novel tyrosine kinase inhibitor of multi-targets, including VEGFR, FGFR, PDGFR, RET and KIT. A phase Ⅰ clinical trial has shown that Lenvatinib had 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), 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, 54% of Grade 3), hand-foot syndrome (61%,7% of Grade 3), proteinuria (59%, 20% of Grade 3), anorexia (57%, 2% of Grade 3), thrombocytopenia (50%, 33% of Grade 3) and fatigue (48%, 0% of Grade 3). 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, is under way, with completion of patient recruitment[22].

***Apatinib***

Apatinib is a novel oral multi-kinase inhibitor of the vascular endothelial growth factor receptor-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 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 were 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 were elevated aminotransferase, thrombocytopenia, elevated bilirubin, hypertension, leukocytopenia, handand-foot syndrome and 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, evaluates 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 in a 2:1 ratio to 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 obvious toxicity profile. The incidence rate of grade 3 and 4 adverse event reached as high as about 80%. 4 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 which suffered from adverse events had to receive dose modifications. A phase II study is currently underway to explore efficacy of refametinib monotherapy on advanced RAS- mutated HCC.

***C-MET inhibitors***

Proto-oncogene c-MET can encode the hepatocyte growth factor (HGF) receptor. The binding of HGF and 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 inhibitors in oral form. Similar to vincristine, it induces disruption of microtubules to exert antitumor effect[28]. A phase Ⅰ b study has investigated for safety profile on 20 patients whose liver functions were scored 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 4 cases receiving sunitinib). In this study, researchers randomly allocated patients at a ratio of 2:1 to receive tivantinib (360mg BID) or placebo. The primary endpoint was TTP, and the secondary endpoint was progression free survival (PFS), OS and RR. Because of high incidence of severe neutropenia after recruitment of 57 patients (38 patients in 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 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 ≥ 2+ in ≥ 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 mmTTP, mOS and 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 dosage of 240 mg BID as an option for second-line treatment of patients with advanced HCC.

It have been carrying out that a placebo-controlled phase III clinical trial to assess 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 the anti-tumor effects through targeted inhibition of MET, VEGFR-2 and RET signaling pathway. Based on the favorable results of a phase III study[32], cabozantinib has been FDA approved for the treatment of advanced medullary thyroid carcinoma. A phase II clinical trial[33] has been performed to explore 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% patients (2/36) was confirmed PR. DCR at 12 wk was 68%; AFP of 38% patients (10/26) with abnormal AFP at baseline was decreased by more than 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 inhibitor***

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 TKI 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 high safety profile and 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 studied.

***TGF-β inhibitor***

Transforming growth factor beta (TGF-β) is closely related to occurrence and development of HCC. Inhibiting this signal transduction pathway may effects 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 more than 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 pazopanib has 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 DCE-MRI, 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 end point with 42.3% tumor control at 16 weeks (> 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 stratification subgroups. The toxicities were acceptable.

**SYSTEMIC CHEMOTHERAPY**

For patients with advanced HCC, systemic chemotherapy used to clinically conduct as a palliative method. Before publication of the EACH study, there were no standard drugs or regimen can be regarded as the golden standard. There was also 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 are used clinically. Additionally, with the optimization of clinical trials and the achievements got from trials, the traditional concept that HCC is unsuitable for chemotherapy has been questioned or challenged. Many researchers have actively investigated 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***

We have conducted an open, multicenter randomized controlled phase III clinical trial for the treatment for 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 patients (11%). Patients were randomly divided into two groups, one group receiving FOLFOX 4 treatment, the other group receiving 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 months *vs* 4.97 months, *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, m OS was significantly prolonged in FOLFOX4 group in comparison with doxorubicin group (5.9 months to 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 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 common used drug doxorubicin acting as a positive control, the EACH study was significantly different to two other phase III trials of sorafenib (both using placebo as control) and was more in line with the requirements of clinical practice and medical ethics. The primary endpoint, of showed improved OS trend, and improved secondary endpoints 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 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 12th, 2013, Chinese Food and Drug Administration (CFDA) formally approved the OXA-containing FOLFOX4 regimen for treatment of advanced HCC. So OXA became the first cytotoxic drug that was officially approved by the governmental drug administration for HCC chemotherapy worldwide.

***GEMOX***

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% patients had become eligible for curative-intent therapies because of down staging, 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 the 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 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) 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 ADM (1 study). Four studies had also added the bevacizumab (Avastin) or cetuximab. The RR was 16.8% (95%CI：12.8-21.6%) in all studies, 20% in GEMOX regimen and 15% in 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 months and 20% in Western patients. 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. So researchers have seen that 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 were worse.

Liu *et al*[48] also reported another meta-analysis. Besides the above-mentioned databases, authors retrieved 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 of more than 30 cases. Finally, twelve studies, in which two were randomized controlled ones, were studied 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 group, 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%; In Western patients group, 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%.

The above two meta-analyses also have some limitations. Except for the EACH study, all studies were single arm ones without 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 the 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 benefits 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 were randomized to receive doxorubicin 60 mg/m2 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 months (95%CI: 7.1-12.9) for doxorubicin plus sorafenib, and 10.5 months (95%CI: 7.4-14.3) for sorafenib with a hazard ratio (HR) 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 got and blood AFP dropped to normal. Subsequently the patient underwent radical surgery. In a randomized, controlled, phase II clinical study (GOTEXT study), Eric 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). 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 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 months, 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 are 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% were with HBV infection, 90% with BCLC stage C and 80% with extrahepatic metastasis, were enrolled in their study. All patients received SECOX regimen (sorafenib, 400 mg b.i.d. day 1-14; OXA, 85 mg/m2 day 1 and Cap 1700 mg/m2 day 1-7 in 2-wk cycles). The primary endpoint was TTP, and second endpoints were RR, PFS, OS and tolerance. The result have shown RR was 16%, SD (lasted at least 8 weeks) was 62%, and mTTP, mPFS and mOS was 5.29 mo, 5.26 mo and 11.73 mo, respectively; the most common grade 1-2 adverse events were diarrhea (75%), hand foot skin reaction (73%) and liver function abnormal; 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 etc. 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 them can induce immune reaction against HCC and then strengthen 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 which 18 completed assessments. The most common adverse reactions were itching, with only 1 patient withdrawing due to pneumonia. His DFS was 16 mo. Ten 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 that 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 is also being 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 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 were 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% 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, twenty-six were due to disease progression, and two due to drug-related adverse events and the rest achieved complete response (CR). A total of 32 patients (68%, furthermore 19% were grade 3/4) developed different grades of drug-related adverse events, 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 incidence more than 5% were elevated AST (11%), elevated ALT (9%) and elevated serum lipase (6%). Of forty-two 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 recombination 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 the low dose group (14 cases) and the high dose group (16 cases). Researchers injected JX-594 direct into patients’ liver tumors at day 1, 15 and 29. After injection, JX-594 gene was detected in their serum. The results showed median survival duration was significantly related to dose (median survival of 14.1 mo compared to 6.7 mo with low dose, respectively; HR = 0.39, *P =* 0.02). In both groups RR were 15% with modified Response Evaluation Criteria in Solid Tumors (mRECIST) and 62% with Choi standard, respectively, even in distant non-injected tumors. A randomized, controlled study is ongoing to compare efficacy of JX-594 and best supportive care for advanced HCC patients who were refractory to sorafenib. And 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 argininosuccinate 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 agent under studied. A phase I/II study[69] of ADI-PEG 20 showed a favourable safety profile in patients with unresectable HCC. In Asian pretreated patients with advanced HCC, ADI-PEG 20 also showed a promising DCR and mOS with mild toxicities, deserves 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 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 researches 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 the phase III studies. Studies of C-MET inhibitors on patients whose lesions are of high expression 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 with immunotherapy, especially immune checkpoint inhibitors, have showed a surprising effect and further clinical trials with 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 part of multidisciplinary approaches for advanced HCC treatment. They aren’t able to cure HCC. In order to get maximal or expected benefit, it should be rationally combined together with different drugs or regimens. HCC is still a big challenge and a severe health problem for the Chinese 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, economic condition and so on 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 deepening of studies, improvement of treatment level, experience accumulation and optimization of treatment strategies, we look forward to get a much better prognosis of advanced HCC.

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**P-Reviewer:** Mihaila BG, Yoshida K, Zhao HT **S-Editor:** Yu J

**L-Editor:** **E-Editor:**

**Table 1 Randomized phase III clinical trials of targeted drugs completed 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.