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REVIEW

Chemotherapy and target therapy for hepatocellular carcinoma: New advances and challenges

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Abstract

Primary liver cancer is one of the commonest causes of death. Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancers. For patients with unresectable or metastatic HCC, conventional chemotherapy is of limited or no benefit. Sorafenib is the only systemic treatment to demonstrate a statistically significant but modest overall survival benefit, leading to an era of targeted agents. Many clinical trials of targeted drugs have been carried out with many more in progress. Some drugs like PTK787 showed potential benefits in the treatment of HCC. Despite these promising breakthroughs, patients with HCC still have a dismal prognosis. Recently, both a phase Ⅲ trial of everolimus and a phase Ⅱ clinical trial of trebananib failed to demonstrate effective antitumor activity in advanced HCC. Sorafenib still plays a pivotal role in advanced HCC, leading to further explorations to exert its maximum efficacy. Combinations targeted with chemotherapy or transarterial chemoembolization is now being tested and might bring about advances. New targeted agents such as mammalian target of rapamycin inhibitors are under investigation, as well as further exploration of the mechanism of hepatocarcinogenesis.

Key words: Hepatocellular carcinoma; Ramucirumab; Regorafenib; Tivantinib; Molecular targeted therapy; Sorafenib; Linifanib; Erlotinib; Everolimus; Sunitinib; Brivanib

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Core tip: Sorafenib is the first drug and now the only systemic treatment to prolong overall survival benefit in patients with hepatocellular carcinoma. In recent years, many molecular targeted agents have been developed and tested. This review article aims to summarize the efforts of systemic therapeutic options and explore the potential new systemic options for this disease.

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INTRODUCTION

Liver cancer is a dominant health problem around the world. It was estimated as the sixth most common cancer in 2012 (782000 new cancer cases worldwide, 5.6% of the total) and the second major cause of cancer death in 2012 (746000 deaths, 9.1% of the total), in accordance with the World Health Organization GLOBOCAN database. Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancer. The incidence is geographically related, as is the mortality, with Eastern and South-Eastern Asia and Western Africa having a high incidence.

HCC can be treated curatively with surgical resection or liver transplantation if diagnosed early; however, since the majority of HCC patients are diagnosed at an advanced stage, their median survival times are generally less than 1 year, leading to a poor prognosis. Only 15% are eligible for curative treatment[1]. The 2 year recurrence rate can reach up to 50%, even for patients undergoing surgery, with a 10 year rate of 76%[2]. One of the primary reasons for the poor prognosis in HCC patients is the absence of potent therapies, particularly in the advanced stage. Cytotoxic and hormonal agents, parts of systemic treatment, have been studied previously and benefited these patients rarely. Not until the recognition of sorafenib have unresectable or advanced patients of HCC had a global standard treatment. With the advent of sorafenib, systemic therapy for these patients has entered a new era of molecular targeted therapy. While initial responses have been observed, a loss of efficacy is apparent over time, which may be due to "resistance" *via* escape/compensatory mechanisms. The prognosis of HCC is still poor. Thus, new treatments and agents are eagerly needed. In this review article, we will take a journey through the history of systemic therapeutic options for HCC, passing through the current standard options and exploring the potential new systemic options for this disease.

CHEMOTHERAPY

In terminal stage HCC, chemotherapy treatment is not routinely used as it is chemorefractory and because of adverse events (AEs). Numerous research has reported 10%-20% response rates for chemotherapeutic agents in HCC. However, chemotherapeutic agents have shown their limited usage because of toxicities. Poor hepatic reserves make it more difficult to endure. Anthracyclines, such as doxorubicin, demonstrated response rates ranging from 0% to 79% but the elevated toxicity restricts its use[3].

Lacking advantage as a monotherapy, several combination regimens have been studied. The combination PIAF [cisplatin, interferon, doxorubicin and 5-fluorouracil (5-FU)] regimen received, a combination of cisplatin, interferon, doxorubicin and 5-FU, received positive results with a median overall survival (OS) of 8.9 mo[4]. However, results of a subsequent study comparing PIAF with doxorubicin alone were disappointing. This study failed to meet its primary endpoint (OS: 8.6 mo *vs* 6.8 mo, $P = 0.83$), displaying meaningless survival benefit[3]. In a retrospective multicenter study of combination gemcitabine with oxaliplatin (GEMOX) in advanced HCC, GEMOX demonstrated effective antitumor effects by obtaining 8 mo OS with manageable toxicity. An overall response rate (ORR) of 22% and disease control rate (DCR) of 66% were observed[5]. Another phase Ⅲ study was conducted to evaluate the role of FOLFOX4 (infusional fluorouracil, leucovorin and oxaliplatin) in terminal HCC patients. This palliative chemotherapy was disappointing and failed to meet its primary endpoint. FOLFOX4, compared with doxorubicin alone, displayed no survival benefit (OS: 6.40 mo *vs* 4.97 mo, $P = 0.07$)[6].

To date, chemotherapy (single agents or combination) has been tested in abundant clinical studies in advanced HCC, but no conspicuous persuasive efficacy in prolonging survival, usually a few months, has been shown. This abominable prognosis and the weak tolerance make new medical therapies an urgent need. Various studies have been conducted to test targeted agents, single or in combination, to improve the outcome of patients with HCC. In a randomized phase Ⅲ trial in patients with advanced HCC (Child-Pugh A) treated with doxorubicin plus sorafenib or doxorubicin alone, the combination chemotherapy resulted in a greater median time to progression (TTP) (6.4 mo *vs* 2.8 mo; $P = 0.02$), OS (13.7 mo *vs* 6.5 mo; $P = 0.006$) and PFS (6.0 mo *vs* 2.7 mo; $P = 0.006$) when compared to doxorubicin monotherapy[7]. Results from another combination therapy (phase Ⅱ, bevacizumab, capecitabine and oxaliplatin) also revealed an encouraging efficacy, with 6.8 mo PFS and 9.8 mo OS[8]. This improvement implied that target agents and chemotherapy probably act synergistically but we need further investigations to be clear about the effectiveness of these treatments.

MOLECULAR TARGETS IN HCC

Without standard treatment, evaluating novel therapeutic options for patients with advanced HCC has become an interesting area for further investigation due to a high unmet medical need. Basic science researchers have made efforts to delineate a better profile of the oncogenic processes and signaling pathways that regulate tumor cell proliferation, differentiation, angiogenesis, invasion and metastasis, which has resulted in the promotion of molecular targeted therapies progress. Within the past several years, many new targeted agents have been researched in clinical studies, some available for medical treatment. However, sunitinib, brivanib, linifanib and

TSU-68 have all had disappointing results in advanced-stage HCC. Efficacies of targeted agents are listed in Table 1.

VASCULAR ENDOTHELIAL GROWTH FACTOR/VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR, PLATELET-DERIVED GROWTH FACTOR RECEPTOR AND FIBROBLAST GROWTH FACTOR RECEPTOR

Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF)-2 are established proangiogenic factors and have a key role in the development of HCC, a hypervascularized tumor that may be especially vulnerable to angiogenesis inhibition.

Sorafenib

Sorafenib, a multikinase inhibitor targeting the Raf serine/threonine kinases and the VEGF receptor 1-3 (VEGFR1-3), PDGF receptor (PDGFR)-b, c-Kit, fms-like tyrosine kinase-3 (FLT-3) and p38 tyrosine kinases[9], was the first approved molecular targeted agent that demonstrated survival benefits in patients with advanced HCC in 2007. Two landmark phase Ⅲ studies, SHARP and the Asia-Pacific trials, showed sorafenib to be a significant progress in the treatment of HCC. The SHARP trial demonstrated that sorafenib (400 mg bid) benefited 602 patients with advanced HCC who had received no systemic treatment previously. Sorafenib prolonged OS when compared with placebo (10.7 mo *vs* 7.9 mo, $P < 0.001$), as well as the median time to radiological progression (5.5 mo *vs* 2.8 mo; $P < 0.001$). Drug-related AEs were diarrhea, weight loss, hand-foot skin reaction and hypophosphatemia[10]. In the Asia-Pacific region study of sorafenib, 226 patients who had not received previous systemic therapy in advanced HCC were randomly assigned to receive either sorafenib (400 mg) or placebo twice per day in 6 wk cycles. In this trial, sorafenib showed an antitumor effect with prolonging OS (6.5 mo *vs* 4.2 mo, sorafenib *vs* placebo, $P = 0.014$) and the TTP (2.8 mo *vs* 1.4 mo, sorafenib *vs* placebo, $P = 0.0005$). AEs were accordance with references[11].

Sorafenib combined with transarterial chemoembolization

Despite initial responses to sorafenib and similar to other targeted agents, most HCC patients experience loss of efficacy and the situation of advanced HCC treatment was still dismal, with less than 1 year of survival. Conventional transarterial chemoembolization (cTACE) is a method that improves[12,13] survival, with rates of 75% at 1 year, 47% at 2 years and 26% at 3 years[12]. Drug-eluting bead (DEB)-TACE is an improvement of cTACE in drug delivery to raise drug concentration and reduce the systemic drug[14,15]. It appears to significantly exceed the antitumor efficacy of conventional TACE, with higher response rates ranging from 70% to 80%, meanwhile decreasing the AEs[16,17]. A high incidence of recurrence is a limitation of TACE, probably because of the up-regulation of VEGF and PDGFR, which in turn increases tumor angiogenesis. As a result, the combination of TACE with antiangiogenic targeted drugs has emerged as an improvement, aiming to reduce post-TACE angiogenesis and the incidence of systemic disease and, as much as possible, improving locoregional therapy efficacy. A clinical trial of sorafenib combined with DEB-TACE (A phase Ⅱ study) in patients with advanced HCC showed considerable efficacy, with a 90% to 100% DCR and 58% objective response and tumor size reduced by 4% (from 6.0 to 5.8 cm; $P = 0.05$) after one cycle combination therapy[18]. Several clinical trials have also shown promising results for combination targeted agents with TACE. One prospective non-randomized controlled trial comparing the efficacy of sorafenib in combination with TACE with TACE alone in unresectable or advanced HCC revealed that the coactions of sorafenib prolonged TTP (6.3 mo *vs* 4.3 mo; $P = 0.004$) and the median OS (7.5 mo *vs* 5.1 mo; $P = 0.009$)[19]. Likewise, another retrospective large scale multicenter study of 222 patients showed antitumor efficacy, with a 12 mo OS and 8.5 mo TTP for the sorafenib combination with TACE for advanced HCC. With these exciting positive results, sorafenib in combination with TACE appears to be a potent treatment for advanced HCC patients[20].

Sorafenib combined with chemotherapy or targeted agents

In studies of sorafenib compared with placebo, sorafenib decreased tumor size less obviously. However, chemotherapy shrinks the true volume of tumor, in spite of the lack of compelling evidence in benefiting survival for advanced patients. This implies the benefit of the combination regimen of sorafenib with a chemotherapeutic agent. Accordingly, many phase Ⅱ/Ⅲ clinical trials have been launched globally to compare "sorafenib plus" combination to sorafenib monotherapy[7]. Unfortunately, the "sorafenib plus" combination has failed to show superiority in clinical trials. The Nexavar-Tarceva combination therapy, a phase Ⅲ study of combination sorafenib with erlotinib (SEARCH) (NCT00901901), had no survival benefit (OS: 9.5 mo *vs* 8.5 mo, $P = 0.204$), according to the study report at the European Society for Medical Oncology (ESMO) Congress in 2012 in Vienna.

Other antiangiogenic therapies

Beyond sorafenib, sunitinib is a fresh multi-targeted tyrosine-kinase inhibitor showing efficacy in gastrointestinal stromal tumors (GIST)[21], advanced renal cell carcinoma[22] and advanced pancreatic neuroendocrine tumors[23]. Sunitinib shows evidence of modest anti-tumor activity with manageable AEs in several clinical trials in patients with advanced HCC[24-26]. The futility and safety reasons of sunitinib forced a phase Ⅲ trial

Table 1 Efficacy results of targeted therapies used in advanced hepatocellular carcinoma treatment

	Trial	Dosage	OS (mo)	PFS/TTP (mo)	AEs	Ref.
VEGF/VEGFR						
Sorafenib	Phase Ⅲ (SHARP) *vs* placebo	400 mg bid	10.7 *vs* 7.9	5.5 *vs* 2.8	HFSR, hypophosphatemia, diarrhea	[10]
	Phase Ⅲ (Asian)	400 mg bid	6.5 *vs* 4.2	2.8 *vs* 1.4	HFSR, diarrhea, hypertension	[11]
	+ TACE *vs* TACE alone	400 mg bid	7.5 *vs* 5.1	6.3 *vs* 4.3	HFSR, alopecia, diarrhea	[19]
	+ TACE	400 mg bid	12	8.5	HFSR, diarrhea, rash	[20]
Sunitinib	Phase Ⅱ	37.5 mg/d	9.8	TTP 4.1	Leukopenia/neutropenia, thrombocytopenia, AST elevation	[24]
	Phase Ⅱ	50 mg/d	8.0	5.3	HFSR, neutropenia, asthenia, thrombocytopenia,	[25]
	Phase Ⅱ	50 mg/d	5.8	2.8	Fatigue, nausea, liver failure, encephalopathy	[26]
	Phase Ⅲ *vs* sorafenib	37.5 mg/d	7.9 *vs* 10.2	4.1 *vs* 3.8	HFSR, thrombocytopenia and neutropenia	[27]
Brivanib	Phase Ⅱ	800 mg/d	10	2.8	Fatigue, hypertension, and diarrhea	[30]
	First-line					
	Phase Ⅱ	800 mg/d	9.79	2.7	Fatigue, hypertension, nausea and diarrhea	[31]
	Second-line					
	Phase Ⅲ (BRISK-PS) *vs* placebo	800 mg/d	9.4 *vs* 8.2	4.2 *vs* 2.7	Fatigue, asthenia, hypertension	[32]
	Phase Ⅲ (BRISK-FL) *vs* sorafenib	800 mg/d	9.5 *vs* 9.9	4.2 *vs* 4.1	Hyponatremia, AST elevation, fatigue	[33]
Vatalanib (PTK787)	Phase Ⅰ/Ⅱ (+ doxorubicin)		7.3	PFS 5.4 mo	Mucositis, alopecia, neutropenia and neutropenic sepsis	[38]
Linifanib	Phase Ⅱ	0.25 mg/kg	9.7	3.7	Diarrhea, hypertension and fatigue	[35]
TSU-68	Phase Ⅰ/Ⅱ	400 mg bid	13.1	2.1	Hypoalbuminemia, diarrhea, anorexia	[40]
EGF/EGFR						
Cediranib	Phase Ⅱ	45 mg /d	5.8	2.8	Fatigue, anorexia and hypertension	[42]
	Phase Ⅱ	30 mg /d	11.7	PFS 5.3 mo	Hypertension hyponatremia and hyperbilirubinemia	[43]
Erlotinib	Phase Ⅱ	1500 mg/d	13		Skin rash, diarrhea, fatigue	[51]
	Phase Ⅱ	1500 mg/d	10.75		Diarrhea, folliculitis, fatigue	[52]
Cetuximab	Phase Ⅱ	250 mg/m^2	9.6	PFS 1.4 mo	Elevated AST, fever, hypomagnesemia	[48]
	Phase Ⅱ (+ gemcitabine + oxaliplatin)	250 mg/m^2 + 1000 mg/m^2 + 100 mg/m^2	9.5	PFS 4.7 mo	Thrombocytopenia, neutropenia, and anemia	[49]
Lapatinib	Phase Ⅱ	1500 mg/d	6.2	PFS 2.3 mo	Diarrhea, fatigue, and elevations of AST/ALT	[54]
	Phase Ⅱ	1500 mg/d	12.6	PFS 1.9 mo	Diarrhea, nausea and rash	[55]
IGF/IGFR						
Cixutumumab	Phase Ⅱ	6 mg/kg weekly	8.0	4-mo-PFS 30%	Diabetes, elevated of AST/ALT, hyponatremia	[59]
PI3K/Akt/mTOR						
Everolimus	Phase Ⅰ/Ⅱ	5 mg/d or 10 mg/d	8.4	PFS 3.8 mo	Lymphopenia, hyponatremia aspartate transaminase,	[70]
	Phase Ⅲ *vs* placebo	7.5 mg/d	7.56 *vs* 7.33	2.96 *vs* 2.6		[71]
Sirolimus	Phase Ⅱ	20 mg/wk	26.4 wk	15.3 wk	Fatigue, ascites, acne, mucositis	[72]
Met						
Tivantinib	Phase Ⅱ *vs* placebo	360 mg bid	6.6 *vs* 6.2	1.6 *vs* 1.4	Neutropenia, anemia, asthenia	[87]
		cMet-high	7.2 *vs* 3.8	2.7 *vs* 1.4		

OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; mTOR: Mammalian target of rapamycin; PI3K: Phosphatidylinositol-3-kinase; Met: Met proto-oncogene; EGFR: Epidermal growth factor receptor; HFSR: Hand-foot skin reaction; EGF: Epidermal growth factor; TACE: Transarterial chemoembolization; AEs: Adverse events; BRISK-PS: Brivanib study in patients at risk-post sorafenib; AST: Aspartate transaminase; ALT: Alanine transaminas; IGF: Insulin-like growth factor; IGFR; Insulin-like growth factor receptor.

(NCT00699374) to stop, which compared sunitinib (37.5 mg/d) with sorafenib (400 mg bid) in patients with advanced HCC. In this study, for sunitinib and sorafenib, respectively, median OS was 7.9 mo *vs* 10.2 mo, median progression-free survival (PFS) was 3.6 mo *vs* 3.0 mo and TTP was 4.1 mo *vs* 3.8 mo. The trial revealed that sunitinib failed to demonstrate superiority or non-inferiority to sorafenib in extending patients' lives with advanced HCC and was associated with more frequent and severe AEs than sorafenib[27].

Brivanib inhibited both VEGFR and FGF receptor (FGFR) signaling pathways[28] and revealed encouraging anti-tumor activity in a preclinical study in which brivanib significantly suppressed five of six patient-derived xenograft HCC models resistant to sorafenib and phase Ⅱ clinical trials[29-31]. Brivanib as first-line agent in advanced HCC patients did not reach the planned primary endpoint with a 6 mo PFS rate of 18.2% and 2.7 mo PFS but demonstrated an encouraging OS of 10 mo and 51% DCR, respectively. The 2.8 mo TTP in this study was comparable with that reported in the Asia-Pacific region sorafenib study (2.8 mo). Notably, the 10 mo OS was higher than the 6.5 mo OS in the Asia sorafenib study[30]. Nevertheless, the large randomized phase Ⅲ brivanib study in patients at risk (BRISK) HCC trials conducted to evaluate the role of brivanib was disappointing again. The BRISK-PS (brivanib-post sorafenib) trial evaluated brivanib *vs* placebo in patients who progressed on/after or were intolerant to sorafenib (NCT00825955) and failed to meet the primary endpoint of improving OS statistically (9.4 mo *vs* 8.2 mo, P = 0.3307)[32]. The BRISK-FL study (NCT00858871) compared the efficacy and safety of brivanib with sorafenib in patients with advanced HCC who had not received systemic therapy before. This research was also disappointing. It failed to meet the primary endpoint in improving OS (9.5 mo *vs* 9.9 mo, brivanib *vs* sorafenib), showing non-inferiority for brivanib *vs* sorafenib. Secondary endpoints of TTP, ORR and DCR were similar in both study arms[33].

Linifanib (ABT-869), a multitargeted tyrosine kinase inhibitor, inhibits the members of the VEGFR and PDGFR families[34]. Linifanib as single agent showed clinical antitumor activity in OS (9.7 mo) and TTP (3.7 mo)[35]. ABT-869 appeared to benefit HCC patients, with an acceptable safety profile. Accordingly, a randomized phase Ⅲ trial to evaluate the efficacy and tolerability of linifanib as first-line therapy *vs* sorafenib (NCT01009593) was conducted and is ongoing in 1035 advanced HCC patients who had no prior systemic therapy. This trial failed to meet its primary endpoint, showing a similar OS in linifanib and sorafenib (9.1 mo for linifanib *vs* 9.8 mo for sorafenib). Longer TTP favored linifanib (5.4 mo *vs* 4.0 mo)[36].

Vatalanib (PTK787), a tyrosine kinase inhibitor that binds directly to the ATP-binding sites of VEGFR, inhibits both FLT-1 and Flk-1/KDR and other class Ⅲ receptor tyrosine kinases, such as PDGFR-β, FLT-4, c-kit and c-fms[37]. A phase Ⅰ/Ⅱ research of vatalanib combined with intravenous doxorubicin in advanced HCC was conducted, resulting in a 7.3 mo OS and 5.4 mo PFS. This was the first coactions trial of protein tyrosine kinase (PTK) and intravenous doxorubicin that demonstrated potent efficacy in advanced HCC patients and provided the basis for further clinical trials combining antiangiogenic agents together with chemotherapy to augment the efficacy[38]. A preclinical trial showed that the coactions of PTK/ZK and interferon/5-FU markedly controlled tumor growth both in cell lines and a xenograft HCC model[39]. Attempting to combine vatalanib with another agent may be a potent agent in HCC management.

TSU-68, a tyrosine kinase inhibitor of PDGFR, FGFR and VEGFR, has revealed promising preliminary efficacy in a phase Ⅰ/Ⅱ trial of heavily pretreated advanced HCC patients, with a 13.1 mo OS and 2.1 mo TTP[40]. Another trial combining TSU-68 with TACE in patients with advanced HCC showed a trend towards prolonged PFS; however, this observation was not statistically significant[41]. A subsequent randomized phase Ⅲ study of combining TACE with either TSU-68 or placebo conducted in Japan, South Korea and Taiwan is currently recruiting patients with unresectable HCC.

Cediranib (AZD2171) is another multitargeted inhibitor of VEGFR, c-kit, PDGFR-β and FLT-4. In a phase Ⅱ clinical trial of cediranib (45 mg/d) in advanced HCC patients, cediranib was not effective at this dose and schedule due to the high incidence of toxicity reactions. A 5.8 mo OS and 2.8 mo TTP were observed[42]. A subsequent phase Ⅱ study of a reduced cediranib dosage (30 mg/d) showed modest antitumor efficacy in advanced HCC with a different tolerability profile. Results of the 5.3 mo PFS and 11.7 mo OS in this group were compared favorably to data reported with 45 mg/d dosing of cediranib in advanced HCC (2.8 mo TTP and 5.8 mo OS). Longer duration of treatment at 30 mg/d dosing and patient selection bias might have contributed to different results[43].

Bevacizumab, an anti-VEGF monoclonal antibody, was the first angiogenesis inhibitor to be approved as an antineoplastic agent. Bevacizumab has shown encouraging effects both as a single agent and in combination with cytotoxic drugs (gemcitabine, oxaliplatin and capecitabine) or erlotinib in several phase Ⅱ trials in patients with advanced HCC[8,44-46]. One trial of bevacizumab combined with erlotinib resulted in a 9.0 mo PFS and 15.65 mo OS, showing significant, clinically meaningful antitumor activity. A 62.5% 4 mo PFS (primary endpoint) was observed[45]. Another phase Ⅱ randomized trial (NCT00881751) is now ongoing, testing sorafenib *vs* bevacizumab and erlotinib.

Ramucirumab (IMC-1121B, LY3009806), a fully humanized monoclonal antibody directed against the extracellular domain of VEGFR-2, is a new therapeutic option that selectively inhibits human VEGFR-2 with a much greater affinity than its natural ligands. An early phase Ⅱ clinical trial of ramucirumab has shown

its encouraging anticancer effect, demonstrating a 69% DCR, 4.0 mo median PFS and 12.0 mo OS in 42 patients with advanced or metastatic liver cancer. The majority of patients enrolled in this trial have well-preserved liver function. An interesting aspect in this trial is the observed OS stratified by liver function difference, showing longer OS favoring ramucirumab Child-Pugh B group than Child-Pugh A group (18.0 mo *vs* 4.4 mo, both are barcelona clinic liver cancer-C)[47]. This positive study spurred the initiation of REACH (NCT01140347). REACH is a large, second-line, randomized phase Ⅲ trial testing ramucirumab in pretreated patients with advanced stage HCC. Five hundred and forty-four hepatocellular carcinoma patients whose disease progressed during or following first-line therapy with sorafenib who were randomized to either ramucirumab or placebo. However, according to the preliminary results released at the ESMO Congress in 2014, ramucirumab was disappointing as it failed to show superiority in terms of OS when compared with placebo (9.2 mo *vs* 7.6 mo, ramucirumab *vs* placebo).

EPIDERMAL GROWTH FACTOR RECEPTOR, INSULIN-LIKE GROWTH FACTOR RECEPTOR AND HEPATOCYTE GROWTH FACTOR/CELLULAR-MESENCHYMAL TO EPITHELIAL TRANSITION FACTOR SIGNALING

Epidermal growth factor receptor (EGFR) is frequently overexpressed in HCC, confirmed by many preclinical trials. Drugs targeting EGFR consist of anti-EGFR antibodies (like cetuximab) and inhibitors of EGFR tyrosine kinases (like erlotinib, lapatinib).

Cetuximab (IMC-C225, ERBITUX) is a recombinant chimeric immunoglobulin G1 monoclonal antibody targeting the extracellular domain of EGFR. A phase Ⅱ clinical trial of cetuximab was conducted to test its safety and efficacy in patients with advanced stage liver cancer. This study failed to show satisfactory results, with no patients obtaining a complete or partial response. Despite its safe toxicity profiles, this trial was also not sufficiently powered to demonstrate a significant benefit given its premature termination due to poor accrual (OS: 9.6 mo, PFS: 1.4 mo). Patients showed good tolerance[48]. The results of another research comparing GEMOX in combination with cetuximab are awaited[49].

Erlotinib (Tarceva, OSI-774) specifically inhibits the EGFR/human epidermal-growth-factor receptor 1 (HER1) which proved to have an important role both in cell lines and animal models of hepatocellular carcinoma[50]. Results of a phase Ⅱ clinical trial testing erlotinib monotherapy in patients with advanced stage liver cancer suggested a benefit with erlotinib manifested by 59% disease control. A 13 mo OS was observed, supporting its anticancer activity[51]. The other clinical study of erlotinib alone showed modest efficacy with 43% DCR in HCC, as well as a weak prolonged OS (10.75 mo)[52]. In contrast to previous positive results with erlotinib, the SEARCH trial, a randomized trial protocol that combined sorafenib with erlotinib for HCC patients, failed to exhibit positive results, revealing that erlotinib when added to sorafenib did not prolong OS in advanced HCC, according to the report of the ESMO Congress in 2012.

Lapatinib, inhibitor of EGFR and HER2/NEU by docking into the ATP binding site of the two receptors, showed no or little efficacy in advanced HCC patients in clinical trials[53]. In one study, lapatinib did not meet the predefined efficacy rate, with the response rate of 5%, and likely did not have significant activity in HCC, with a 2.3 mo PFS and 6.2 mo OS[54]. Results from the other study revealed modest activity of lapatinib based on the lack of objective responses (primary endpoint of this study), short median PFS (1.9 mo) and relatively modest proportion of patients with stable disease (40%). A 12.6 mo OS was observed[55].

Insulin-like growth factor (IGF) signaling has been widely studied in preclinical trials and its dysregulation in liver cancer by up-regulating IGF-2 and down-regulating IGF-2 receptor has been witnessed[56]. Strategies to target this signaling consisting of monoclonal antibodies and small molecule inhibitors against IGF-1R are still being researched. To date, unfortunately all IGF-R antibodies demonstrate no benefit in advanced HCC. Equally disappointing results were also reported from a phase Ⅱ clinical trial of cixutumumab (IMC-A12), a fully human IgG1 monoclonal antibody that binds specifically to IGF-R1[57]. It inhibits tumor cells growth and apoptosis in a human tumor xenograft model by effectively blocking ligand-induced phosphorylation[58]. However, results from the phase Ⅱ study indicated that IMC-A12 monotherapy is ineffective, with a 8.0 mo OS and a 4 mo PFS rate of 30%[59]. BIIB022 is a non-glycosylated monoclonal antibody for IGF-1R[60]. A phase Ⅰ/Ⅱ research was halted early because of a business decision by the sponsor company.

Mitogen-activated protein kinase pathway (retrovirus-associated DNA sequences/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase)

The rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway primarily participates in cell growth, survival and differentiation and is up-regulated in HCC[61,62]. Targeting RAF kinase is one of the most promising targeted approaches for the medical management of HCC. Sorafenib is also a strong inhibitor against the Raf serine/threonine kinases, the pro-angiogenic receptor tyrosine kinases VEGFR, PDGFR and FGFR1, and tyrosine kinases[63]. Selumetinib (AZD6244) is a non-ATP competitive small molecular inhibitor of the MAPK mitogen-activated protein kinase kinase (MEK) 1/2[64]. A phase Ⅱ trial of selumetinib, the first study of

an inhibitor of MEK in HCC, conducted in patients with advanced or metastatic liver cancer pretreated with systemic therapy showed depressing results due to a lack of response in radiography and short PFS (8 wk). There was no difference in TTP and a 4.2 mo OS was observed. This research was discontinued prematurely when a planned interim analysis was conducted[65].

PI3K/Akt/mammalian target of rapamycin pathway

The PI3K/AKT/mammalian target of rapamycin target protein (mTOR) signal pathway is especially active in HCC and indirectly modulates angiogenesis through regulation of VEGF expression and translation of proteins involved in angiogenesis[66]. mTOR exists widely in various biological cells and is considered to regulate tumor proliferation and metabolism directly or indirectly[67]. mTOR inhibitors (such as everolimus and sirolimus) are not traditionally considered as direct angiogenesis inhibitors; rather, they have well-known immunosuppressive properties and are applied to prevent rejection in organ transplant recipients[68].

Everolimus (Certican, RAD 001), an oral specific mTOR, showed antineoplastic properties in both cell lines and patient tissues derived HCC tumors in murine xenograft models *via* mTOR regulation of tumor proliferation and metabolism[69]. In phase Ⅰ/Ⅱ testing, everolimus resulted in a 3.8 mo PFS and 8.4 mo OS in advanced HCC patients, showing preliminary antitumor activity. This study had a 44% DCR[70]. Everolimus has different antitumor activities and signaling pathway compared to sorafenib and it should be effective in patients who do not respond to sorafenib. However, the latest results from a phase Ⅲ trial combining everolimus with placebo (EVOLVE-1 study) declared the failure of everolimus with non-improvement of OS in advanced HCC patients failed with or intolerant to sorafenib. In this study, the median OS in the everolimus arm was 7.56 mo *vs* 7.33 mo in the placebo arm (P = 0.675). The median TTP was 2.96 mo *vs* 2.6 mo (everolimus *vs* placebo). There was no benefit in the median TTP, in the overall population or in any of the pre-stratified subgroups[71]. A phase Ⅰ/Ⅱ research comparing the combination of everolimus and sorafenib with sorafenib alone was conducted to test the efficacy of the everolimus combination regimen and the results of this trial are awaited (NCT01035229).

Sirolimus exhibited some antitumor activity in a phase Ⅱ study in patients with advanced liver cancer, showing an OS of 26.4 wk. The median time to radiological progression was 15.3 wk[72]. Further trials are needed to assess the value of sirolimus in HCC.

COMPOUNDS IN DEVELOPMENT FOR TREATMENT OF HCC

Nintedanib (BIBF 1120) is an orally available, small, multiple receptor tyrosine kinase inhibitor of VEGFR 1-3, FGFR and PDGFR. BIBF 1120 clearly inhibited tumor growth and angiogenesis in a xenograft model and exhibited relatively mild effects on HCC cell lines *in vivo*[73-75]. Results from a phase Ⅲ study in patients with advanced recurrent non-small cell lung cancer who had failed with first-line chemotherapy showed that nintedanib notably benefited patients with adenocarcinoma in median PFS and OS, including those with a poor prognosis (NCT00805194)[76]. Combination regimen of nintedanib with carboplatin and paclitaxel for medical management of advanced ovarian cancer is ongoing (NCT01015118). As for hepatocellular carcinoma, nintedanib is still being researched to compare the safety and efficacy with sorafenib (NCT00987935 and NCT01004003).

Regorafenib (BAY 73-4506) is a structurally unique inhibitor targeting multiple cancer-associated kinases, including angiogenic (VEGFR1-3, TIE2), stromal (PDGFR-β, FGFR) and oncogenic receptor tyrosine kinases (KIT, RET and RAF)[77,78]. Regorafenib improved the management of metastatic colorectal cancer patients who failed with standard treatments[79], thus leading to the FDA approval of regorafenib. Regorafenib treatment demonstrated a notable benefit in PFS when compared to placebo in metastatic GIST that failed with standard management[80]. A phase Ⅱ clinical trial testing the efficacy of regorafenib as a second-line drug in patients with liver cancer who progress after prior sorafenib treatment showed positive results in terms of TTP (4.3 mo) and OS (13.8 mo)[81]. A phase Ⅲ study is currently ongoing (NCT01774344).

The hepatocyte growth factor (HGF)/mesenchymal to epithelial transition factor (Met) pathway is well known to involve in tumor growth, angiogenesis and invasion in various types of cancer. Cellular-Met is a tyrosine kinase receptor for the HGF ligand. HGF inducing activation of c-Met ultimately results in the activation of downstream effecter molecules, including phospholipase C, PI3K and ERK. In early gene array studies, elevated expression of c-Met was demonstrated to be related to the poor accrual and short OS in patients with liver cancer[82-84].

A current focus of interest for HCC drug development is the c-Met inhibitor tivantinib (ARQ197). Tivantinib, a selective MET receptor, inhibits MET activation and demonstrated antitumor activity in human HCC and other tumor cell lines, as well as in human tumor xenograft models[85,86]. A highly publicized phase Ⅱ trial has provided hope for tivantinib as a potential second line candidate after sorafenib failure, particularly in high c-Met HCC. Results from this study demonstrated nearly doubling the median PFS in high c-Met patients (2.7 mo *vs* 1.4 mo tivantinib *vs* placebo; P = 0.03) and the median OS (7.2 mo for high c-Met patients on tivantinib *vs* 3.8 mo for high c-Met patients on placebo; P = 0.01). Longer TTP was observed in the tivantinib arm than placebo (1.6 mo *vs* 1.4 mo; P = 0.04). There was no difference in median OS (6.6 mo *vs* 6.2 mo, tivantinib *vs* placebo, P = 0.63). Initially a high incidence of neutropenia in this study led to a dose reduction from 360 mg bid to 240 mg bid[87]. This study provides a proof of concept that personalized targeted therapy is paving its way in the field of HCC research. In the

two currently ongoing phase Ⅲ trials (NCT01755767 for the European/United States trial, NCT02029157 for the Japanese trial), tivantinib is being tested in patients with sorafenib failure against best supportive care and placebo. Despite initial problems with severe neutropenia in the European/United States trial due to a change in the drug formulation used in the phase Ⅲ trial compared to the phase Ⅱ trial, this study is currently ongoing and is actively recruiting patients.

Besides tivantinib, there are other c-Met inhibitors undergoing clinical testing, such as cabozantinib, Inc-280 and refametinib. Cabozantinib (XL184), a dual blockade of VEGFR2 and MET, inhibited tumor growth in HCC by decreasing angiogenesis, inhibiting proliferation and promoting apoptosis, but it exhibited more profound efficacy in phosphorylated-MET positive HCC xenografts[88]. A phase Ⅲ study of cabozantinib *vs* placebo in HCC patients who have received prior sorafenib (NCT01908426) is ongoing. A similar targeted approach is being taken with the MEK-inhibitor refametinib (BAY 86-9766) in Ras-mutated HCC. Refametinib, a highly selective and potent small molecule allosteric (non-ATP-competitive) inhibitor of MEK 1 and MEK 2, showed potent single agent antitumor activity and acted synergistically in combination with sorafenib in preclinical HCC models, albeit with potential application for only a small subgroup of HCC patients[89-91]. Refametinib in two single-arm phase Ⅱ trials (first line combined with sorafenib: NCT01915602 and second line *vs* placebo: NCT01915589) and another c-Met inhibitor Inc-280 in a first-line phase Ⅱ trial are under investigation (NCT01737827).

FUTURE PERSPECTIVES

HCC is a complex causal disease and the prognosis of HCC patients remains poor, especially for advanced HCC. Researchers have shown the contribution of signaling pathway abnormalities to tumor progression and growth. In the coming years, the development of molecular targeted therapy that specifically inhibits angiogenesis factors will be a domain direction in the treatment of HCC with the advent of sorafenib. Targeted agents that inhibit angiogenesis factors simultaneously with inhibition of other key proangiogenic factors in HCC, such as FGFR or c-MET signaling, has provided further insights into the underlying pathogenesis of HCC tumors. Compounds of dual inhibition that block angiogenesis and tumorigenesis directly and other compounds that indirectly modulate angiogenesis are providing novel mechanisms that exploit critical pathways in HCC tumor progression and may have the potential to improve clinical outcomes, both as monotherapy and in the case of escape from sorafenib.

To date, sorafenib is the sole systemic medical management option demonstrating a significant antitumor effect for advanced HCC. Several new promising multi-targeted molecules have been found and are currently under research for the improvement of liver cancer. Unfortunately, HCC are refractory to many targeted therapies. For this reason, resistance to molecular targeted agents is a major challenge for now and in the future. Combination therapy, including various drugs or a single inhibitor of cellular pathways, may provide improvement to overcome this resistance challenge. Targeted agents, combined with either multiple targeted agents or conventional chemotherapeutic agents, may be more effective and require to be further explored. Combination regimens of sorafenib with other targeted drugs are being researched. Sorafenib was a major breakthrough and is still effective, ignoring the drug resistance. To move beyond sorafenib monotherapy, a potential role for this agent in the adjuvant setting following surgical resection, radiofrequency ablation, TACE or in combination with other targeted agents or chemotherapy is under investigation.

Novel pathways and molecular targets undergoing clinical trials are required to define its efficacy in the adjuvant, neoadjuvant and metastatic setting. Exploring the mechanism of hepatocarcinogenesis is also needed to expound its molecular pathogenesis and to confirm other key targets for intervention. Future development of genomic analysis of HCC for the identification of both specific predictive and prognostic biomarkers will be a leap, increasing promise for HCC patients.

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