

Systemic treatment of hepatocellular carcinoma: Past, present and future

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Abstract

Hepatocellular carcinoma (HCC) is a common neoplasia which represents the second leading cause of cancer related death. Most cases occur in developing countries, but its incidence is rising in Western countries due to

hepatitis C. Although hepatitis therapies have evolved and the HCC screening has increased in several areas, 40% present with advanced disease which is only amenable for palliative systemic treatment. HCC continues posing a challenge, in part due to the inherent chemoresistance of this neoplasia, the pharmacologic challenges due to an ill liver, difficulty in assessing radiological responses accurately, *etc.* Traditional chemotherapy have shown some responses without clear survival benefit, however, sorafenib demonstrated advantages in survival in advanced HCC when liver function is kept and recently immunotherapy seems to be a promising approach for some patients. This article will briefly expose the most relevant systemic treatment modalities to offer a general view from the past to the future.

Key words: Hepatocellular carcinoma; Alphafetoprotein; Sorafenib; Nivolumab; MEK

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Core tip: The incidence of hepatocellular carcinoma (HCC) is rising in Western countries due to hepatitis C. Unfortunately, 40% of patients present with advanced disease which is only amenable for palliative systemic treatment. The development of effective therapies for HCC is a challenge, due partly to its inherent chemoresistance, the pharmacologic challenges due to an ill liver, *etc.* Although some responses to traditional chemotherapy have been reported, the multikinase inhibitor sorafenib has shown survival benefit in advanced HCC with preserved liver function. Recently immunotherapy seems to be a promising approach for some patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a hepatic neoplasia that occupies the second place as cause of cancer related deaths^[1]. It appears most frequently in a liver with chronic injury and cirrhosis^[2] and it is usually diagnosed as an advanced stage with a poor median survival rate (6-20 mo)^[3].

Its incidence varies depending on geographical zones and races. This is mainly related to differences in incidences of hepatitis B and C. The highest rates are seen in Asia (where hepatitis B incidence is very high) and Africa, though increasing in developed areas due to hepatitis C^[4]. Other risk factors include steatohepatitis, alcoholic liver disease, aflatoxins and hemochromatosis.

Unfortunately 40% of diagnosis will present with an advanced disease with the only options of systemic therapy in most of them^[5]. HCC nowadays continues to pose a significant challenge to the therapy, in part due to poor chemosensitivity (expression of drug resistance genes) and the liver dysfunction which hinders the delivery of these drugs. Moreover, cirrhosis will have an impact on the drug distribution volumes^[6].

Although newer treatments have appeared, the survival rates of advanced HCC patients have not yet significantly improved.

HCC is an aggressive tumour whose treatment possibilities will depend on the phase of the tumour, the liver functionality and patient's performance status. There are several staging systems available^[7-9] but no consensus on which to use. The Child-Pugh system will assess the patient's hepatic reserve and liver function. Other staging systems, such as Barcelona Clinic Liver Cancer, will consider tumour phase, performance status, hepatic status, symptoms, etc. This system may provide the link between disease and treatment strategies. In very early/early stages, curative treatment (liver surgery or hepatic transplantation) and locoregional treatments (such as radiofrequency ablation), have better survival benefits.

Intermediate stage is very heterogeneous and transarterial chemoembolization/radioembolization are the main options if preserved hepatic function (Child-Pugh A) and performance status 0.

Advanced cases have got a short prognosis. For these patients, systemic palliative therapies might be considered.

This article will briefly expose the most relevant systemic treatment modalities to offer a general view from the past to the future.

CYTOTOXIC CHEMOTHERAPY: MONOTHERAPY

HCC is poorly chemosensitive due to the expression of drug resistance genes, and the liver dysfunction which hinders the delivery of drugs. In the past years, no single treatment or regimen have shown superiority to another^[10].

Glutathione-S-transferase, topoisomerase II α , p-glycoprotein, heat shock proteins, and p53^[11-17] are related to chemotherapy sensitivity. Most published studies with chemotherapy have shown RRs of less than 25% and there is no evidence of improvement in OS^[18-20]. However, chemotherapy may still be an option after progression on sorafenib if good performance status and preserved liver function.

Nagahama *et al*^[21] carried out a study in 147 HCC patients in first line. Results showed that those cases affected by severe cirrhosis, tumour involving > 50% of the liver, ECOG performance 2-3 and tumour thrombus in the portal vein do not respond to chemotherapy.

Doxorubicin has been used since the 1970s. A study carried out in Africa enrolled 14 patients and found a 79% of responses^[22]. However, posterior trials showed much less RR (10% to 20%)^[23,24].

It is not clear whether doxorubicin prolongs survival. A single study with 60 cases randomised to doxorubicin vs no treatment and it demonstrated a significant extension in survival (10.6 wk vs 7.5 wk, $P = 0.036$) favouring doxorubicin^[25]. Later a meta-analysis comparing doxorubicin to no treatment or other treatments did not find a survival benefit^[26]. Another randomized study comparing doxorubicin against nolatrexed, found better survival with doxorubicin (32.3 wk vs 22.3 wk, $P = 0.007$) but the authors concluded that results could be biased due to more patients failed to continue treatment with nolatrexed due to side-effects^[27].

Several phase II trials with other anthracyclines did not show any significant benefits over doxorubicin in outcomes or toxicity^[28-31] (Table 1).

5-fluorouracil (5-FU) and other fluoropyrimidines have been used in HCC. 5-FU has undergone extensive evaluation in HCC and shown RRs in the range of 10%^[32,33]. 5-FU bolus with leucovorin showed higher gastrointestinal adverse effects, and responses of 0%-28%^[33,34].

Capecitabine is a prodrug that is converted at the site of the tumour to 5-FU. Its toxicity profile appears to be more manageable^[35], but RRs remain relatively low^[36]. A retrospective study by Patt *et al*^[35] investigated the role capecitabine in 63 patients (37 HCC). Capecitabine in HCC showed a RR of 1% with an OS of around 10 mo. Most frequent adverse events included hand-foot syndrome and thrombocytopenia^[35]. Jiang *et al*^[37] have reported a high activity of dihydropyrimidine dehydrogenase in liver cancer. This could impact on the chemoresistance to these chemotherapy agents. In the adjuvant setting, Xia *et al*^[38] carried out a randomized, controlled trial with capecitabine after HCC operation. Sixty patients were randomized to capecitabine or control. Results favoured the capecitabine arm with a lower recurrence rate (53.3% vs 76.7%), longer median time to recurrence (40 mo vs 20 mo, $P = 0.046$) and higher 5-year OS (62.5% vs 39.8%, $P = 0.216$) with tolerable side effects^[38].

Gemcitabine is another chemotherapy drug which appears to be very active *in vitro* (HCC cell lines). However, several clinical studies have shown limited activity^[39].

Table 1 Doxorubicin as first line treatment in hepatocellular carcinoma

Ref.	n	Line/treatment	Relevant data
Nagahama <i>et al</i> ^[221]	147	First line doxorubicin	Severe cirrhosis, PS 2-3, tumour occupying > 50% liver do not respond to chemo
Olweny <i>et al</i> ^[222]	14	First line doxorubicin	RR 79%
Sciarrino <i>et al</i> ^[223]		First line doxorubicin	RR 10%-20%
Chlebowski <i>et al</i> ^[241]			

RR: Response rate.

Only one small study (28 patients) reported by Yang *et al*^[40] showed a RR of 17%. The subsequent trials have only shown RRs of 0%-2%^[41,42]. Cisplatin is a platinum analog that has demonstrated a 15% of responses as monotherapy^[43].

CYTOTOXIC CHEMOTHERAPY: COMBINATION

In an attempt to increase the rate of clinical benefits, several combinations of chemotherapy have been studied but to date none has proven superiority when compared with single agents. This is very important as combinations are more toxic and thus clinicians should weigh the toxicity against any added palliative benefit they hope to get.

The EACH is a phase III, open-label study comparing FOLFOX4 (infusional FU, leucovorin, oxaliplatin) vs doxorubicin in 371 patients with advanced HCC. FOLFOX4 showed a higher RR (8.15% vs 2.67%, $P = 0.02$), disease control rate (DCR) (52.17% vs 31.55%, $P < 0.001$), longer PFS (2.93 mo vs 1.7 mo, $P = 0.001$; HR = 0.62) and OS (6.40 mo vs 4.97 mo, HR = 0.80; $P = 0.07$)^[44].

Shin *et al*^[45] reported a trial of cisplatin combined with capecitabine and doxorubicin in 25 patients. They found a RR of 26% and around 1/3 of patients showed a significant reduction in alfa-fetoprotein (AFP) levels, though this reduction is not a reliable marker for clinical benefit. This study mentioned toxicity only briefly with one treatment-related death. Lee *et al*^[46] carried out a study with the combination of cisplatin and doxorubicin. This phase II trial showed responses in the line of 19%, with around 1/3 of the patients having a significant reduction of AFP. Significant neutropenia was reported in 14.3%.

Combinations of platinum derivatives and gemcitabine seem to be more effective with tolerable adverse events if hepatic function is acceptable. Gemcitabine and oxaliplatin have shown responses of 15%-20% and stabilizations of 48%-58% in small studies^[47,48].

A retrospective study in 204 patients with advanced HCC treated with a combination of gemcitabine and oxaliplatin (GEMOX) was reported in 2011 ASCO meeting. Fifty-one percent had Child Pugh A, 20.6% Child Pugh B, and 4.4% Child Pugh C. The results showed a RR of 22% and DCR of 66%. PFS, TTP and OS of 4.5, 8 and 11 mo. Authors found that if an objective response was seen, OS was higher (19.9 mo vs 8.5 mo). Grade 3/4 toxicity occurred in 44.1% and most frequent adverse events were diarrhoea, neutropenia, thrombocytopenia

and neuropathy^[48]. In addition, 8.5% became candidates for curative treatments thanks to responses. Moreover, the response to GEMOX, among other factors, was independently associated to OS.

Patrikidou *et al*^[49] carried out a retrospective study of GEMOX as second line. Forty patients were included after failure of one anti-angiogenic treatment minimum. Severe adverse events were found 25% of the cases. Partial response was observed in 20% of patients, while 46% had stable disease.

Median OS was 8.3 mo and survival rate at 6 mo was 59%. Median PFS was 3.1 mo. Performance status, baseline AFP levels and BCLC score were independently associated with OS. Another study has demonstrated RR of 21% with cisplatin and gemcitabine but with 1/3 of the patients suffering from severe neutropenia and 1/4 significant thrombocytopenia^[50]. Another trial with cisplatin, 5-FU and mitoxantrone found RR of 27% with 71% patients with severe neutropenia^[51].

Docetaxel plus gemcitabine showed a 10% RR and unacceptable hematologic toxicity^[52]. Irinotecan has shown minimal effectiveness with significant adverse events, so its use is not advisable^[53,54] (Table 2).

HORMONAL THERAPY

As there is a significant male predominance in morbidity and mortality in HCC, it has long been considered that sex hormones play a role in its development. Some HCCs express estrogen receptors (ER) and estrogens have shown some protective effects against HCC.

Tamoxifen, a competitive antagonist of the estrogen receptors, have been studied in several clinical trials to assess its activity against HCC but only a little benefit in response or survival has been found^[55,56].

Megestrol acetate blocks wildtype and variant forms of ERs and it has been assessed in HCC with variant ER. Benefits varied according to trials. Whereas some of them showed some benefits, a study of megestrol acetate vs placebo as first line of advanced HCC did not prolong OS^[57-60].

Octreotide is a somatostatin analogue and around 40% of hepatic carcinomas express these receptors. Octreotide has shown direct antitumor effect in HCC^[61,62]. Several studies have shown different benefits but a metaanalysis showed survival rates at 6 and 12 mo higher than those seen in the other arms, though only in Eastern studies^[63]. However, these results are still controversial.

Table 2 Clinical trials with chemotherapy agents in hepatocellular carcinoma

Ref.	n	Treatment	Results
Lai <i>et al</i> ^[25]	60	Doxorubin <i>vs</i> placebo	OS 10.6 wk <i>vs</i> 7.5 wk in favour of chemo
Gish <i>et al</i> ^[27]		Doxorubicin <i>vs</i> nolatrexed	OS 32.3 wk <i>vs</i> 22.3 wk in favour of doxorubicin
Patt <i>et al</i> ^[35]	37	Capecitabine	RR 1%, OS 10.1 mo
Qin <i>et al</i> ^[44]	371	FOLFOX 4 <i>vs</i> doxorubicin	RR 8.15% <i>vs</i> 2.67% DCR 52.17% <i>vs</i> 31.55% PFS 2.93 m <i>vs</i> 1.7 m OS 6.4 m <i>vs</i> 4.97 m
Shin <i>et al</i> ^[45]		Cisplatin, Capecitabine and Doxorubicin	RR 26%
Lee <i>et al</i> ^[46]		Cisplatin/doxorubicin	RR 19%
Zaanani <i>et al</i> ^[48]	204	GEMOX	RR 22% DCR 66% PFS 4.5 m OS 11 m
Patrikidou <i>et al</i> ^[49]	40	GEMOX after antiangiogenics failed	Partial responses 20% Stable disease 46% OS 8.3 m
Yang <i>et al</i> ^[50]		Cisplatin/gemcitabine	RR 21%
Kim <i>et al</i> ^[52]		Cisplatin/infusional FU/mitoxantrone	RR 27% but 71% severe neutropenia

RR: Response rate; DCR: Disease control rate; PFS: Progression free survival; OS: Overall survival.

MOLECULARLY TARGETED THERAPY

Carcinogenesis is a complex process involving multiple signalling cascades. Sorafenib is a small inhibitor of several tyrosine protein kinases (TKI), such as VEGFR, platelet derived growth factor receptor (PDGFR) and Raf family kinases. It will inhibit growth of multiple kinases related to angiogenesis, cell proliferation and differentiation^[64,65]. In preclinical studies, sorafenib has shown antiproliferative effects in HCC cell lines. It also decreased tumour angiogenesis and tumour-cell signalling, increasing apoptosis in a mouse model^[65].

Abou-Alfa *et al*^[66] carried out an uncontrolled phase II study with sorafenib in advanced HCC and Child-Pugh A or B. Results favoured sorafenib with OS of 9.2 mo and a TTP 5.5 mo.

A large phase III, multicenter, randomized, double-blind, placebo controlled trial (SHARP trial) was undertaken in advanced HCC. Six hundred and two patients naïve for treatment, were randomized to sorafenib or placebo. This study showed an OS of 10.7 mo *vs* 7.9 mo in favour of sorafenib, with a hazard ratio of 0.69; 95%CI: 0.55 to 0.87; $P < 0.001$). Both groups were similar in the median time to symptomatic progression (4.1 mo *vs* 4.9 mo, $P = 0.77$).

Two percent of partial responses were seen in patients with sorafenib and 1% in the placebo; overall toxicity was similar between the treatment and placebo arm (52% *vs* 54%), though diarrhoea, hand-foot syndrome, weight loss and hypophosphatemia were more prominent with sorafenib.

Another phase III placebo controlled trial was carried out in Asian patients (Oriental study). Two hundred and twenty-six patients with Child-Pugh A cirrhosis and no prior systemic treatment were randomized to sorafenib or placebo. Sorafenib showed significantly longer median OS (6.5 mo *vs* 4.2 mo) and median TTP (2.8 mo *vs* 1.4 mo)^[67].

Sorafenib in combination with chemotherapy has been examined. A study compared doxorubicin with sorafenib

vs doxorubicin alone^[68]. The combination prolonged median TTP (6.4 mo *vs* 2.8 mo, $P = 0.02$), PFS (6.0 mo *vs* 2.7 mo, $P = 0.006$) and median OS (13.7 mo *vs* 6.5 mo, $P = 0.006$)^[68]. CALGB80802 study^[69] recruited patients with advanced HCC, naïve for palliative treatment and Child-Pugh A. The patients received either doxorubicin 60 mg/m² every three weeks plus sorafenib or sorafenib monotherapy. After 346 patients the study was halted. An interim analysis reported that the combination arm produced higher toxicity and did not improve OS^[69]. Other studies were designed to evaluate the combination of GEMOX regimen and sorafenib. A randomized, controlled, phase II trial (GOTEXT), compared sorafenib and GEMOX combined with sorafenib as first-line treatment. Ninety-four patients were randomized. The results showed that RRs, DCRs, PFS and median OS were 9% *vs* 70%, 16% *vs* 77%, 54% *vs* 61%, and 13 mo *vs* 13.5 mo, respectively, favouring the combination^[70].

Sorafenib combined with oxaliplatin has shown good activity in phase II trials but requires further investigation in larger randomized clinical trials. Regorafenib is a multi-kinase inhibitor which has shown activity against HCC. Bruix *et al*^[71] carried out a study, open-label, phase II, multicenter, to assess safety and efficacy of regorafenib in patients diagnosed with advanced HCC after failure with sorafenib. Thirty-six patients were included and disease control was achieved in 26 with one partial response. TTP and OS of 4.3 and 13.8 mo respectively and a tolerable safety profile. Most frequent side effects were fatigue, hand-foot syndrome and diarrhoea.

The phase III trial (RESOURCE, NCT01774344) showed a benefit for regorafenib with longer median progression-free survival (3.1 mo *vs* 1.5 mo) compared to placebo. OS (primary end point) was 10.6 mo *vs* 7.8 mo in favour of regorafenib. Overall, authors found that 65.2% of patients on regorafenib showed complete/partial response or stable disease, compared to 36.1% in the placebo group. Side effects were similar to those reported with sorafenib namely hypertension, hand-foot skin reaction, fatigue and

diarrhea^[72].

Cabozantinib is a multiple receptor tyrosine kinases inhibitor, including HGF receptor [mesenchymal-epithelial transition (MET)], Ret, and the VEGF receptor. A phase II trial which included 41 patients with HCC has shown promising results^[73]. These patients had Child-Pugh A and had progressed to a previous systemic therapy. Patients on cabozantinib showed 5% of partial responses, 78% stable disease, and 7% progressive disease, with a median OS of 15.1 mo and median PFS of 4.4 mo, regardless of previous treatment with sorafenib. Most frequent side-effects grade 3 or higher were diarrhea, palmar-plantar erythrodysesthesia, and thrombocytopenia.

A multinational phase III clinical trial, CELESTIAL, has been planned to recruit 760 patients with advanced HCC after progression on sorafenib. Patients will receive cabozantinib daily or placebo (randomization 2:1). The trial is expected to show data in 2017^[74,75]. The endpoints are OS (primary), RR and PFS.

Lenvatinib is a multitargeted (VEGFR, PDGFR, RET, FGFR and KIT) tyrosine kinase inhibitor. The recommended dose was 12 mg daily in Child-Pugh A (5-6 score) and 8 mg in Child-Pugh B (7-8 score)^[76].

A phase II clinical trial, multicenter, evaluated lenvatinib in advanced HCC. Patients receive 12 mg once daily in 28-d cycles. The primary endpoint was TTP. Forty-six patients were included in Japan and South Korea showing TTP of 7.4 mo (95 %CI: 5.5-9.4).

Thirty-seven percent had partial response and 41% stable disease (DCR 78%). Median OS was 18.7 mo (95%CI: 12.7-25.1). Frequent adverse events such as hypertension (> 75%), palmo-plantar syndrome (> 60%), reduced appetite (> 60%) and proteinuria (> 60%). Dose reductions in 74% and treatment was stopped in 22%, due to adverse effects. Authors found that median body weight was lower in patients with an early (< 30 d) dose withdrawal or reduction.

This study concluded that lenvatinib shows clinical activity with acceptable toxicity but early dose modification is needed if low body weight. Further studies should consider this^[77].

The pivotal Phase III REFLECT trial comparing lenvatinib to sorafenib has been completed, and its results will determine whether lenvatinib represents another potential option. A clinical trial of lenvatinib vs sorafenib in naïve patients will recruit 1000 patients with unresectable HCC and its completion is estimated for later this year^[78].

Tivantinib is a selective small MET tyrosine kinase inhibitor with antitumor activity, especially in MET-high patients. Its activity is due to a disruption of microtubules^[79]. An initial study in 20 patients with Child-Pugh A or B^[80] found that most relevant side-effects were fatigue (> 1/2), anorexia, alopecia and diarrhoea (15% each). Serious neutropenia (38%) and anaemia (24%) were seen, which implies that a careful haematological monitoring is needed during the treatment.

A phase II randomised trial in second line has been carried out. Patients were stratified by circulating levels of MET, hepatocyte growth factor and levels of alpha-

fetoprotein. Circulating levels of MET were related to prognosis as OS was 4.6 mo in high levels vs 8.9 mo if low (HR = 0.61; $P = 0.023$). If low MET tumours, TTP, OS or DCR did not show differences.

This trial found relevant toxicities such as grade 3 anemia (9%), neutropenia (6%) and thrombocytopenia (6%). This led to a dose recommendation of 240 mg BID for second-line.

MET expression was also correlated with sorafenib as 40% of biopsies taken prior to sorafenib therapy were MET-high compared with 82% after sorafenib. A significant interaction in OS between tivantinib and MET expression was reported ($P = 0.039$). The other biomarkers examined were not predictive of tivantinib response^[81].

A phase III, randomized, double-blind trial in second line, after progression on sorafenib is ongoing in HCC patients with high-expression of MET. The endpoints include OS (primary), PFS and safety. The anticipated study completion date is mid-2017^[81-83].

Ramucirumab is a fully human monoclonal anti-VEGFR-2 antibody. It binds to the receptor with high affinity and prevents ligand activation. HCC has got high expression levels of VEGF which entails worse results^[84]. REACH is a randomized, double-blind trial, in HCC patients refractory or not amenable to locoregional treatments who had failed to sorafenib. OS, which was the primary endpoint, was not significantly different with ramucirumab or placebo (9.2 mo vs 7.6 mo; HR = 0.87; 95%CI: 0.72-1.05; $P = 0.14$). On the contrary PFS was improved as objective RR. Regarding toxicity, most common side effects grade 3 or above were ascites, hypertension, asthenia, and increased aspartate aminotransferase^[85]. When patients were stratified by AFP, OS benefited ramucirumab if AFP > 400 ng/mL (7.8 mo vs 4.2 mo; HR = 0.67; 95%CI: 0.51-0.90; $P = 0.006$). These results suggested that patients with elevated AFP might be more likely to benefit from ramucirumab. A prospective phase III trial, REACH 2, whose completion is estimated for late 2017, will assess the safety and efficacy of ramucirumab as second-line in patients with elevated baseline AFP^[85].

Apatinib is a small-molecule multi-kinase inhibitor of VEGFR-2. Qin *et al*^[86] carried out a phase II dose-finding study in naïve patients with HCC Child-Pugh A. These patients were randomised to apatinib 850 mg/qd or 750 mg/qd. Endpoints TTP (primary), OS, RR, DCR, level of AFP and safety. One hundred and twenty-one patients were recruited. The results showed a median TTP of 4.2 and 3.3 mo for the two different dosages respectively. DCR was 48.57% and 37.25% respectively. Median OS was 9.7 and 9.8 mo respectively. The authors concluded that apatinib produced a survival benefit and both doses were recommended for further study^[86].

Most frequent adverse effects were elevated levels of bilirubin, aminotransferase, blood pressure, thrombocytopenia, leukocytopenia, palmo-plantar erythrodysesthesia, fatigue, but most of them were easily managed by dose interruptions or reductions.

A phase 1/phase 2 trial of apatinib for advanced HCC

Table 3 Clinical trials with tyrosine kinase inhibitors in hepatocellular carcinoma

Ref.	n	Treatment	Results
Abou-Alfa <i>et al</i> ^[66]		Sorafenib	OS 9.2 m TTP 5.5 m
Cheng <i>et al</i> ^[67]	602	Sorafenib vs placebo	OS 6.5 m vs 4.2 m TTP 2.8 m vs 1.4 m
Abou-Alfa <i>et al</i> ^[68]	226	Sorafenib vs doxorubicin	TTP 6.4 m vs 2.8 m PFS 6 m vs 2.7 m OS 13.7 m vs 6.5 m
Assenat <i>et al</i> ^[70]	94	Sorafenib vs sorafenib/GEMOX	RR 9% vs 70% DCR 16% vs 77% PFS 54% vs 61% OS 13 m vs 13.5 m In favour of the combination
Bruix <i>et al</i> ^[71]	36	Regorafenib second line	DCR in 26/36 patients Partial response 1/36 TTP 4.3 m OS 13.8 m
LBA-03 ^[72]		Regorafenib vs placebo	DCR 65.2% vs 36.1% PFS 3.1 m vs 1.5 m OS 10.6 m vs 7.8 m
Verslype <i>et al</i> ^[73]	41	Cabozantinib	Partial response 5% Stable disease 78% PFS 4.4 m OS 15.1 m
Exelixis ^[74,75]	760	Cabozantinib second line (after sorafenib)	Primary end point OS Expected data in 2017
Koyama <i>et al</i> ^[76]	46	Lenvatinib	DCR 78% TTP 7.4 m OS 18.7 m
Eli Lilly and Company ^[85] Qin <i>et al</i> ^[86]	121	Ramucirumab vs placebo Apatinib vs placebo	OS 9.2 m vs 7.6 m TTP 4.2 m vs 3.3 m DCR 48.57% vs 37.25% OS 9.7 m vs 9.8 m

RR: Response rate; DCR: Disease control rate; PFS: Progression free survival; OS: Overall survival; TTP: Time to progression.

after first-line treatment failure (NCT02772029) will be soon recruiting patients. A multicenter, randomised, double blind phase III trial (NCT02329860) was started in December 2014, aiming to assess its activity and toxicity profile after progression on sorafenib and/or chemotherapy. It has planned to recruit 360 patients (randomized 2:1). Primary endpoint is OS. This trial is still ongoing. See all the results in Table 3.

IMMUNOTHERAPY

Recently tumor immunotherapy has evolved rapidly. As most HCC are driven by inflammation, there is a strong rationale to evaluate immunotherapy in these patients.

Pembrolizumab

The single-arm, multisite, phase 2 KEYNOTE-224 study (ClinicalTrials.gov, NCT02702414) was designed to assess the activity and toxicity pembrolizumab in patients with previously treated advanced HCC. This trial plans to recruit 100 patients. The primary end point will be objective RR.

Another single-arm phase II trial of Pembrolizumab in patients with advanced, unresectable HCC is ongoing. Endpoints are DCR (primary), PFS, OS, RR, duration of response and toxicity. Researchers will assess the

expression levels of programmed death-ligand 1 (PD-L1) in tumor tissue, and serum titers of hepatitis B or C in patients with hepatitis B or C, respectively, for whom specimens are available.

Nivolumab

Several tumours express PD-1, among them HCC and this is related with poor prognosis. The union PD-1/PD-L1 block the T cell receptor signal transduction, inhibit proliferation and induce depletion of T cells achieving tumour immune escape. Blocking the PD-1 pathway will promote an antitumoral immune response^[87]. Nivolumab is an anti-PD-1 antibody^[88].

A phase I / II study (Interim analysis of the Check-Mate-040 dose escalation study) in advanced HCC was reported at the 2015 ASCO annual meeting.

Patients with advanced HCC, Child-Pugh ≤ 7, who had failed, declined, or did not tolerate sorafenib were included. Patients had nivolumab 0.1-10 mg/kg every two weeks for a maximum of 2 years. Three parallel cohorts were made depending on hepatitis: No active infection, hepatitis B, hepatitis C. Endpoints were safety (primary), efficacy and RR. Biomarkers assessment was included as an exploratory endpoint.

Fifty-one patients were included. Seventy-three percent of them had prior sorafenib. Twenty-nine percent

Table 4 Clinical trials with immunotherapy in hepatocellular carcinoma

Authors	n	Phase	Treatment	Primary end-point
Keynote-224 ongoing	100	II	Pembrolizumab	RR
CheckMate-040		II	Pembrolizumab	DCR
CheckMate-040		I / II	Nivolumab	Safety
CheckMate-459	726	III	Nivolumab vs Sorafenib	OS TTP

RR: Response rate; DCR: Disease control rate; OS: Overall survival; TTP: Time to progression.

had response or stable disease and most common adverse effects were rash and AST increase. Responses were seen regardless PD-L1 status evaluated by IHC.

Authors concluded that nivolumab showed manageable toxicity with long duration responses or stabilizations regardless dosage or cohorts^[89-91]. CheckMate-040 shows that nivolumab is effective with acceptable toxicity in HCC, regardless hepatitis status.

Another phase III study, CheckMate-459, (NCT02576509) has planned to recruit 726 patients to assess nivolumab compared to sorafenib as first line. Endpoints will be OS, TTP (as primary), RR, PFS, expression of PD-L1 and efficacy. The stratification will observe geographical area, etiology, vascular invasion and extrahepatic dissemination. It is planned to be finished by May 2017.

Tremelimumab

It is a humanized anti T-lymphocyte-associated antigen-4 (CTLA-4) IgG2 antibody which has shown good results in the treatment of 21 patients with hepatitis C^[92]. RR of 18% and DCR of 76%, with TTP of 6.48 mo^[93] were seen.

Transarterial chemoembolization and radiofrequency ablation can also trigger immune activity against HCC and potentiate the anti-CTLA-4 activity^[94].

Twenty patients were included and Duffy *et al*^[94] presented the results in ASCO 2015. Disease free survival was 16 mo and median PFS 7.4 mo. Forty percent of patients treated with transarterial chemoembolization/radiofrequency ablation showed partial response and 5 out of 7 patients with hepatitis C had a significant reduction in viral load. Most frequent side effect was itching and only 1 patient stopped due to pneumonitis. These authors found evidence of immune cells infiltration in tumour biopsies taken at 6 mo. As clinical activity was encouraging, tremelimumab combined with transarterial chemoembolization/radiofrequency ablation has been considered for further investigation^[94] (Table 4).

MEK inhibitors

A relevant signalling pathway in hepatocarcinogenesis is the MEK cascade. This is involved in cellular adaptation and survival. A key role is played by MEK, with MEK 1/2 as interesting targets for new drugs.

Refametinib is an oral MEK inhibitor which has been combined with sorafenib in a phase II trial^[95]. The RR

6.2% and DCR 43%, with a median OS of 9.6 mo. The best response was seen in RAS mutated group. Unfortunately, the rate of grades 3 and 4 side-effects was 80% and 4 patients died due to liver failure, hepatic encephalopathy, tumour lysis syndrome and unknown reason.

Another phase II^[96] of refametinib alone or combined with sorafenib in HCC with mutant RAS was carried out. Patients with HCC, unresectable, Child-Pugh A, no prior systemic therapy for HCC (except prior sorafenib in monotherapy study) were eligible. Patients in the monotherapy trial were treated with refametinib 50 mg bid, while in the combination they were treated with refametinib 50 mg bid and sorafenib 400 mg bid.

Four hundred and ninety-eight patients in the monotherapy and 820 patients in the combination were enrolled. Median PFS was 58 d, median time to radiological progression 84 d, and median OS 177 d. In the combination study no patients achieved a confirmed partial response, median PFS was 46 d, TTP 84 d, and median OS 427 d^[96]. Authors concluded that either monotherapy or combination did not show sufficient efficacy to warrant further development in this group of patients.

Some other some small molecule c-MET inhibitors, such as foretinib^[97] as first line or tepotinib^[98] particularly in C-MET positive tumours, have shown promising activity with high safety profile. The most common side effects were hypertension, fever and anorexia. Capmatinib^[99], golvantinib^[100], and others are also under study^[101].

CONCLUSION

HCC is one of the most frequent worldwide neoplasias and although many efforts have been made to get a prompt detection, many cases are still diagnosed in an advanced stage no amenable to radical treatments. The treatment of an advanced HCC is still challenging and although there are many trials under way to evaluate new drugs targeting different molecular pathways relevant in hepatocarcinogenesis, much knowledge remains still in early stages. Sorafenib improved survival but sorafenib resistance is still a significant issue and several clinical trials assessing other new molecular targeted agents have failed. Regorafenib and lenvatinib showed promising activity in phase II clinical trials and are undergoing evaluation in phase III. Immunotherapy has recently emerged as a promising therapy for many cancers including HCC. Nivolumab has shown benefits and awaits trials to confirm these positive results. Tremelimumab open the door to combination with locoregional treatments and it has also shown a reduction in tumour viral load in hepatitis C^[100].

The efforts will continue and hopefully will soon pay off.

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