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Role of Systemic Therapy and Future Directions for Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive tumor that often arises in the setting of liver cirrhosis. Although early-stage disease is often amenable for surgical resection, transplant, or locoregional therapies, many patients are diagnosed at an advanced stage or have poor liver reserve. Systemic therapy is the mainstay of treatment for these patients. At present, the only approved therapy for the treatment of advanced disease is the tyrosine multikinase inhibitor sorafenib. Candidacy for treatment is based on liver reserve. Novel agents for the treatment of this disease are urgently needed. In this article, we review systemic therapy trials and upcoming data for the treatment of HCC.

Keywords

hepatocellular carcinoma, systemic therapy, clinical trials

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Introduction

Hepatocellular carcinoma (HCC) is an aggressive tumor and is one of the leading causes of cancer-related death worldwide.[1] Around 60% to 80% of patients with HCC have underlying cirrhosis.[2] Risk factors for the development of HCC include viral and nonviral causes of cirrhosis (hepatitis B or C, nonalcoholic steatohepatitis, and alcohol), inherited errors of metabolism (hereditary hemochromatosis, porphyria cutanea tarda, α-1 antitrypsin deficiency, and Wilson disease), environmental exposures (aflatoxin), and primary biliary cirrhosis. Because of the pathogenesis of this disease, the treatment for patients with HCC is often complicated by underlying liver dysfunction.

The mainstay of treatment of early-stage disease is surgical; however, many patients are not surgical candidates due to the extent of tumor or underlying liver disease. Patients with poor underlying liver function and/or unresectable disease that is limited to the liver may meet criteria for liver transplantation.[3,4] Patients who are not candidates for transplantation can be evaluated for liver-directed therapy, including ablation, embolization (bland, chemoembolization, or radioembolization), or stereotactic radiotherapy.

For patients with more advanced disease, systemic therapy is preferred, but there are several challenges to treatment. The etiology of the underlying cirrhosis is often different based on geography and patients may respond differently to treatment. Asian patients tend to have underlying hepatitis B and have well-compensated cirrhosis, whereas Western patients tend to be older with more comorbidities and higher incidence of alcoholic cirrhosis and hepatitis C. Several chemotherapy regimens have been evaluated but have shown very modest efficacy. Targeted therapy has also been tested, and at present, the only Food and Drug Administration (FDA)–approved therapy for the treatment of advanced unresectable HCC is the oral multikinase tyrosine kinase inhibitor sorafenib. Objective tumor response rate is limited with this therapy and clinical trials are

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ongoing to develop more effective treatment strategies for this deadly disease. This review will focus on systemic treatment options including chemotherapy, molecularly targeted therapy, and immunotherapy and future directions for the treatment of HCC.

Chemotherapy

Hepatocellular carcinoma presents several challenges to treatment with chemotherapy in that it is generally chemorefractory and patients often have underlying cirrhosis, making it difficult to treat with agents that undergo hepatic metabolism. Chemorefractoriness is suspected to be in part due to high rates of expression of drug-resistant genes, heat-shock proteins, and p53 mutations.[5-7] Several chemotherapy agents have been investigated.

A study looked at 147 patients with previously untreated HCC, enrolled in phase 2 trials in Japan, to determine predictive factors for tumor response to chemotherapy. Of these, only 10 had a partial response (<10% response rate). Of the patients with poor performance status, ascites, portal vein thrombosis, or serum bilirubin >2, none had any objective response with chemotherapy.[8] However, a more recent study looked at predictive factors in patients undergoing treatment with 5-fluorouracil (5-FU), mitoxantrone, and cisplatin (FMP) therapy and found an objective response rate (ORR) of 22%. Interestingly, the trial found the absence of radiographic intrahepatic disease and ascites to be independent favorable prognostic factors, suggesting that patients with sufficient hepatic function may derive benefit from chemotherapy.[9]

Single-Agent Chemotherapy

Doxorubicin is the most studied chemotherapeutic agent in advanced HCC. Initial studies showed an ORR of 79%; however, subsequent studies have shown ORR of less than 20% with doses of 75 mg/m^2.[10] Few studies have shown an overall survival (OS) benefit with doxorubicin monotherapy and those that did showed an improvement in survival of about 3 weeks compared to best supportive care (BSC).[11] An open-label trial of doxorubicin in combination with high-dose tamoxifen showed 32% response rate, suggesting that tamoxifen may potentiate the effect of doxorubicin, although it showed progression-free survival (PFS) of only 7 months.[12]

5-Fluorouracil has relatively low toxicity, broad anticancer activity, and despite hepatic metabolization, can still be given in the setting of liver dysfunction. One study showed an ORR of 28% in patients with HCC with good performance status, with no significant toxicities.[13] A retrospective study of capecitabine showed a similar ORR of 25% and median OS of 10.1 months with mostly common toxicities such as hand–foot syndrome and thrombocytopenia and was safe even in the setting of cirrhosis.[14] A phase 2 trial of metronomic capecitabine in patients with HCC enrolled both untreated patients and patients previously treated with sorafenib. Previously untreated patients had a PFS of 6 months and an OS of 14.5 months with stable disease in 50% of patients; previously treated patients had a PFS of 3.2 months and an OS of 9.8 months.[15] A randomized phase 2 trial in previously untreated patients compared single-agent capecitabine to sorafenib and showed 2-month OS and PFS benefit in the sorafenib arm, showing capecitabine to be inferior to sorafenib as a single agent.[16]

Table 1. Selected Trials With Single-Agent Chemotherapy.

Chemotherapy	Toxicities	Best Response
Doxorubicin	Myelosuppression, anorexia, nausea/vomiting, alopecia	ORR 79%, median OS of 8 months[10] ORR < 20%[25]
5-FU	Mucositis, diarrhea, neutropenia	ORR as high as 28%[13]
Capecitabine	Hand foot syndrome, thrombocytopenia	ORR of 25%[14]
Irinotecan	Diarrhea	ORR < 10%[18]
Gemcitabine	Cytopenias, hepatotoxicity	18% PR for median duration of 13 weeks[17]

Abbreviations: 5-FU, 5-fluorouracil; ORR, objective response rate; OS, overall survival; PR, partial response.

Single-agent gemcitabine and irinotecan have also been evaluated and shown to have only very modest activity in HCC (Table 1). Weekly gemcitabine achieved a short partial response in only 17% of patients, while other gemcitabine trials in HCC showed no ORR.[17] Irinotecan showed <10% ORR and progressive disease (PD) in all other patients, with considerable toxicities.[18]

Combination Chemotherapy

Chemotherapy combinations have been studied in an attempt to improve response rate and OS compared to single-agent regimens (Table 2). The combination of cisplatin and doxorubicin showed an ORR of 19% and a median OS of 7.3 months.[19] Several other chemotherapy combinations including FMP (infusional 5-FU, mitoxantrone, and cisplatin), ECF (cisplatin, infusional 5-FU, and epirubicin), low-dose FP (continuous 5-FU and low-dose cisplatin), and XELOX (xeloda and oxaliplatin) have been evaluated in phase 2 trials and have shown partial response and stable disease, with ORR ranging from 6% to 18% and OS ranging from 9 to 11 months. A randomized phase 3 trial in Asian patients, with predominantly hepatitis B as the etiology of cirrhosis, compared FOLFOX4 to doxorubicin. Median PFS was significantly better with FOLFOX4 (2.9 vs 1.7 months), and although there was a trend toward improved OS, the primary end point was not met. FOLFOX4 did also have a higher response rate (8% vs 3%) and disease control rate (52% vs 32%), but with some increased rate of neuropathy in the FOLFOX group. Most neuropathy was mild and there was no increase in grade 3 or 4 toxicities in either group.[20]

Several studies have explored gemcitabine-based therapies, with similar ORR as other combinations. A phase 2 study of

Table 2. Selected Trials for Combination Chemotherapy.

Chemotherapy	Common Toxicities	Best Response
FMP	Leukocytopenia, neutropenia, thrombocytopenia, elevated LFTs	PR in 27% with median duration of 7.6 months, 53% with SD[77]
ECF	GI toxicity, hand–foot rash	Median OS of 10 months and ORR of 14.5%[78]
Low-dose FP	Nausea, vomiting	PR in 47%, TTP 211 days[79]
GEMOX	Thrombocytopenia, neutropenia, neurotoxicity	ORR 18%, SD in 58%, median PFS 6.3 months, median OS 11.5 months[22]
XELOX	Diarrhea, elevated LFTs, thrombocytopenia, neurotoxicity	ORR 6%, 72% disease control rate, median PFS of 4.1 months, and OS of 9.3 months[80]
mFOLFOX4	Neuropathy, similar toxicity to low-dose doxorubicin	Median PFS of 2.9 months, ORR of 8%, and disease control rate of 52%[20]
PIAF	Hematologic toxicity	Median OS benefit of 2 months, ORR of 20.9%[25]

Abbreviations: ECF, cisplatin, infusional 5-FU, and epirubicin; FMP, 5-fluorouracil, mitoxantrone, and cisplatin; mFOLFOX, 5-FU, oxaliplatin, leukovorin FP, continuous 5-FU and low-dose cisplatin; GEMOX, gemcitabine plus oxaliplatin; GI, gastrointestinal; ORR, objective response rate; OS, overall survival; PIAF, cisplatin, IFNa, doxorubicin, and infusional 5-FU; PFS, progression-free survival; XELOX, xeloda and oxaliplatin.

gemcitabine and cisplatin showed an ORR of 20%, median OS of 21 weeks, and median duration of response of 13 weeks.[21] A phase 2 trial of gemcitabine and oxaliplatin showed an ORR of 18%, stable disease in 58% of patients, and median PFS and OS of 6.3 and 11.5 months, respectively. This study also noted improved efficacy in patients with nonalcoholic cirrhosis compared to those with alcoholic cirrhosis.[22] Another phase 2 study combined GEMOX (gemcitabine plus oxaliplatin) with bevacizumab, still with an ORR of 20%, 27% of patients with stable disease, and median PFS and OS of 5.3 and 9.6 months, respectively.[23]

The PIAF regimen (cisplatin, IFNa, doxorubicin, and infusional 5-FU) combined chemotherapy and immunotherapy (further discussed below), still with only modestly improved ORR (26%) in a phase 2 study and with significant hematologic toxicity.[24] A phase 3 trial of PIAF compared to doxorubicin showed an ORR of 20.9% with PIAF compared to 10.5% with doxorubicin, but again with significant myelosuppression and hypokalemia. The ORR and OS differences were not statistically significant.[25,26]

Overall, the results of chemotherapy regimens have been relatively disappointing to date with modest ORR of 20% or less. Although it had significant toxicity, the PIAF combination regimen showed the greatest ORR and may be used in noncirrhotic patients with HCC. Median PFS and OS were similar in all of the above treatments, with PFS of about 4 to 6 months and OS 9 to 12 months. While there is no standard of care chemotherapy regimen for HCC, cytotoxic drugs can be considered in selected patients with preserved liver function and good performance status.

Molecularly Targeted Therapy

The molecular pathogenesis of HCC is not well understood; however, several molecularly targeted therapies have been evaluated for activity including inhibitors of vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), and MEK and MET pathway inhibitors. Mutation profiling of HCC has shown about 30 to 40 mutations, of which 5 to 8 are suspected to be driver mutations—amplifications in several oncogenes such as FGF19, VEGFA, CCND1, and TERT have led to several potential targets.[27]

Vascular Endothelial Growth Factor Pathway

Vascular endothelial growth factor inhibition downregulates HGF and therefore decreases proliferation and induces apoptosis. Sorafenib is a multitargeted tyrosine kinase inhibitor that inhibits VEGF, as well as Raf kinase and PDGF receptor, and is currently the only approved therapy for HCC. It was evaluated in the randomized phase 3 SHARP trial which showed a 2.8-month OS benefit of sorafenib compared to BSC (10.7 vs 7.9 months).[28] A second phase 3 trial done in Asia also showed improved median OS with sorafenib compared to placebo.[29] Both of these trials included primarily patients with Child-Pugh (CP) A cirrhosis, and most subsequent trials of other molecular targets have had similar design as the SHARP trial. An exploratory analysis showed the highest survival benefit in patients with hepatitis C, compared to those with hepatitis B or alcohol.[30] Several retrospective analyses compared outcomes in patients with CP A versus B scores and showed improved outcomes with CP A scores (11.3 vs 5.5 months and 9.5 vs 3.2 months). They also noted baseline aspartate transaminase (AST) level to be a significant predictor of survival.[31] Despite shorter OS and higher incidence of serious adverse events and higher rates of death in patients with CP B, the Global Investigation of therapeutic Decisions in HCC and Of its treatment with sorafeNib trial showed similar safety profiles of CP A and B scores.[32] Another retrospective study looked at sorafenib in patients with CP A, B, and C cirrhosis and found a median OS of 8.3, 4.3, and 1.5 months, respectively, suggesting that patients with CP C scores do not benefit from sorafenib.[33]

After approval of sorafenib, there were many studies combining sorafenib with chemotherapy and other targeted therapies, but none have shown significant improvement in outcome (Table 3). A phase 2 trial of sorafenib with doxorubicin showed an ORR of 4% but significantly longer TTP with the combination compared to doxorubicin alone (6.4 vs 2.8 months); however, a phase 3 trial (CALGB 80802) failed to show survival benefit of the combination when compared to sorafenib alone.[31,34] A phase 3 trial of sorafenib with erlotinib also failed to show survival benefit and actually showed worse disease control rate in patients who received the combination.[35]

Other VEGF inhibitors have shown some benefit, although none have been shown to be superior to sorafenib. A phase 2 trial of the anti-VEGF therapy bevacizumab showed 13% ORR

Table 3. Selected Trials for Targeted Therapies.

Drug	Common Toxicities	Best Response
Sorafenib	Diarrhea, weight loss, hand–foot skin reaction	Improved OS (10.7 months vs 7.9 months) compared to placebo[28]
Sorafenib + erlotinib	Fatigue, diarrhea, elevated LFTs	No OS benefit, lower disease control rate with sorafenib + erlotinib[35]
Regorafenib	Hypertension, hand–foot skin reaction, fatigue, diarrhea	Median OS of 10.6 months, ORR 11% and 65% disease control[44]
Bevacizumab	Hypertension, thrombosis, major bleed	ORR 13% and median PFS 6.9 months[36]

Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

and median PFS of 6.9 months. However, 11% of patients had serious bleeding complications.[36] Other phase 2 trials have combined bevacizumab with erlotinib, with conflicting results (ORR of 24% vs 3%),[37,38] and a randomized controlled trial of this regimen in second-line patients with HCC is currently ongoing.[39] Another VEGF inhibitor, sunitinib, has been evaluated in several phase 2 studies and has shown a 35% to 45% rate of stable disease. However, a phase 3 study comparing it to sorafenib showed it to be inferior (median OS of 7.9 vs 10.2 months) and the trial was closed prematurely for failure to show superiority and also increased toxicity (encephalopathy and hepatorenal syndrome).[40] A second-line phase 2 trial of the tyrosine kinase inhibitor axitinib showed promising ORR and tumor control rate; however, there was no OS benefit as compared to BSC.[41] Similarly, the anti-VEGFR2 antibody ramucirumab was evaluated in a phase 3 randomized controlled trial in patients with HCC who had previously been treated with sorafenib and showed improvement in median PFS and TTP relative to placebo but no improvement in OS.[42] Linifanib, an ATP competitive inhibitor of VEGF and PDGF receptor tyrosine kinases, was compared to sorafenib in a large phase 3 randomized trial which included 1035 patients. Although there was a greater ORR with linifanib (13% vs 6.9%), there was no survival benefit.[43] Recently, the ongoing randomized, double-blind, phase 3 trial of regorafenib in patients with HCC progressing on sorafenib (RESORCE) trial randomized patients who had progressed on sorafenib to the oral multikinase inhibitor regorafenib versus placebo. The median OS was 10.6 versus 7.8 months.[44] This agent may become the established second-line therapy for advanced HCC. Of note, 68% of patients required dose adjustments of regorafenib for toxicity.

Epidermal Growth Factor Receptor Pathway

Epidermal growth factor receptor is frequently expressed in HCC and may contribute to its aggressive growth. The anti-EGFR/human epidermal growth factor receptor 1 tyrosine kinase inhibitor erlotinib has been studied in combinations as above, as well as a single agent.[31] Per a systemic literature search of 10 phase 2/3 trials (9 phase 2 trial and 1 phase 3 trial), most studies noted a disease control rate of 42.5% to 79.6% and a median OS of 6.25 to 15.65 months. The most frequent grade 3/4 toxicities were fatigue (11.9%), diarrhea (10%), increased alanine transaminase (ALT) and AST (7.3%), and rash (6.9%).[45] Overall, erlotinib is generally well tolerated, but more clinical trials are needed to evaluate the safety and efficacy of the drug.

The anti-EGFR antibody cetuximab has also been studied in advanced HCC. It has shown a 65% disease control rate when combined with gemcitabine and oxaliplatin during a phase 2 trial of 45 patients. Results showed a response rate of 20% with a median PFS of 4.7 and a median OS of 9.5 months.[46] Another phase 2 trial with the combination of capecitabine, oxaliplatin, and cetuximab noted a partial response of 12.5%, stable disease in 75%, and a disease control rate of 83%. Median time to progression was 4.5 months, and OS was 4.4 months. The combination was associated with a modest response rate but a high radiographic stable disease. However, OS and PFS seem shorter compared to historical numbers of the phase 3 trial with sorafenib.[47] This was a generally well-tolerated regimen, and further studies using cetuximab with a chemotherapy backbone have been undertaken but results are not yet available.[48]

Other Pathways

TGF-β has a known role tumor suppression and progression and has been found to be elevated in a subgroup of HCC tumors. A TGF-β selective TKI galunisertib is currently being evaluated in phase 2 studies alone and in combination with sorafenib. Data from one of these studies have shown a trend toward improved TTP in patients with a greater reduction in AFP and TGF-β.[27] This trend also suggests a possible biomarker associated with targeting this pathway.

Fibroblast growth factor is also frequently overexpressed in HCC and plays a role in proliferation, invasion, and angiogenesis in the liver and has been suggested to also have a role in resistance to anti-VEGF therapy.[49] FGF19 is amplified in 5% to 10% of liver cancers, and preclinical models have shown this amplification to be associated with response to FGF19-targeted antibodies, suggesting another potential biomarker.[27] Brivanib inhibits both FGFR and VEGFR, but is not FGF19 specific, and has been evaluated in 2 phase 3 studies, one in the first-line setting with sorafenib (BRISK-FL) and another in the second-line setting compared to placebo (BRISK-PS). Neither study met the primary objective, although in the second-line setting, brivanib did show longer TTP than placebo (4.2 vs 2.7 months).[50,51] Dovitinib inhibits FGFR, VEGFR, and PDGF receptor and was evaluated in a phase 2 trial comparing it to sorafenib, and although it was well tolerated, it failed to show superiority to sorafenib.[52] Studies of FGFR-specific TKIs such as BGJ398 are currently ongoing.

Phosphorylated MEK can be detected by IHC in all HCCs, and increased phosphorylation and expression of MAPK has been shown in over 90% of HCCs. The RAS pathway has an

important role in proliferation, and mutations are common in several different cancers. In vitro treatment with MEK inhibitors has led to growth inhibition and apoptosis, suggesting that the MEK/MAPK pathway plays a role in HCC pathogenesis and could be a therapeutic target.[53] Several phase 2 trials have looked at MEK inhibitors (selumetinib and refametinib) in HCC and showed median TTP of 122 days and median OS of 290 days; however, no phase 3 trials have been completed to date.[27]

Dysregulated interaction between the MET receptor and HGF occurs during hepatocyte injury and liver regeneration, with MET activation found in 50% of patients with advanced HCC.[27] Hepatocyte growth factor inhibitors or MET inhibitors such as tivantinib and cabozantinib have shown promising antitumor activity as monotherapy and in combination with sorafenib. A phase 2 placebo-controlled randomized trial of second-line tivantinib showed improved median time to progression. This was more pronounced in patients with MET-high tumors (as assessed by IHC).[54] A phase 3 placebo-controlled trials is currently ongoing.[55] Similarly, second-line treatment with cabozantinib has shown preliminary activity,[56] and a placebo-controlled phase 3 study is ongoing.[57]

Molecularly targeted therapies have shown promise in this chemotherapy refractory disease, and current trials may lead to new FDA approvals for this disease, particularly in the second-line setting; however, to date, none have shown superiority to sorafenib, which remains the current standard of care.

Antibodies, Immunotherapy and Vaccines

Certain features of HCC suggest that it would be susceptible to immunologic manipulation. An increased ratio of cytotoxic T cells as compared to regulatory T cells has been associated with improved survival.[58] Initial studies with interferon α (IFNα) in advanced HCC were promising with evidence of disease acitivty,[59] but a recent randomized controlled trial showed IFN to be poorly tolerated in cirrhotics and showed no survival benefit. As discussed above, IFN has also been combined with chemotherapy as part of the PIAF regimen and showed some benefit, but with significant toxicity.

Checkpoint inhibition has also been evaluated in HCC (see Table 4). A phase 1/2 study of nivolumab was performed in patients with CP A or B who had either progressed on or did not tolerate sorafenib. Preliminary data of 47 patients with expansion cohort at 3 mg/kg dose showed 8 patients with objective antitumor response, 2 with CR, and 48% with stable disease.[60] The most recent update of this study, a dose expansion cohort, included 206 participants with advanced HCC and CP A. Preliminary data revealed 50% of patients with treatment-related adverse events, 55% of patients with at least 18 weeks follow-up and/or PD, and 6-month OS rate of 69%.[61] Lastly, a phase 1/2 study of nivolumab investigated patients with advanced HCC who failed, refused, or were intolerant of sorafenib. Forty-eight patients were evaluable for response, and results noted 15% CR, 8% PR, 50% SD, 31% PD with a median OS of 15.1 months.[62]

Table 4. Selected Trials for Immunotherapy.

Drug	Common Toxicities	Best Response
Nivolumab (dose expansion 3 mg/kg)	Fatigue, pruritus, grades 3-4 increased AST/ALT	Preliminary phase 1/2 trial data of 47 patients showed 5% CR, 18% PR, 72% OS at 6 months[62] Follow-up study with 206 noted PD of 55% and OS 6 months survival of 69%[64]
Nivolumab (0.1-10 mg/kg for up to 2 years)	Rash, grades 3-4 increased AST/ALT	Initial phase 1/2 study showed 15% CR, 8% PR, 50% SD, 31% PD, median OS 15.1 months[62]
Pembrolizumab (200 mg IV every 3 weeks up to 35 cycles or PD)	Pending study results	Phase 2 study ongoing, pending final results Primary end point is ORR Secondary end point is OS, safety/tolerability, PFS, CR, PD
Codrituzumab (1600 mg every 2 weeks after 2 loading doses)	Anemia, increased AST	Phase 2 study showed PFS of codrituzumab versus placebo to be 2.6 versus 1.5 months, respectively. OS is 8.7 versus 10 months[70]
Pembrolizumab (200 mg IV every 3 weeks) + BSC versus placebo + BSC up to 35 cycles or until disease progression	Pending study results	Phase 3 study ongoing, pending final results Primary objective is PFS and OS Secondary objective is ORR, CR, PD
Pexa-Vec (10e9 PFU injections every 2 weeks × 3) + sorafenib (400 mg BID starting at week 6) versus sorafenib (400 mg BID from day 1)	Pending study results	Phase 3 study ongoing, pending final results Primary end point is OS Secondary end point is PFS, ORR, CR Safety, biomarkers, and quality of life will be evaluated

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; BSC, best supportive care; CR, complete response; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFU, plaque forming units; PR, partial response.

There are ongoing checkpoint inhibition trials involving pembrolizumab. A phase 2 trial of pembrolizumab plans to evaluate the drug's efficacy in 100 patients with previously treated advanced HCC.[63] Another phase 3 trial compared the efficacy and safety of pembrolizumab with BSC against placebo with BSC in patients with previously treated advanced HCC.[64] A study of durvalumab (a selective PDL-1 inhibitor) and tremelimumab (a CTLA-4 inhibitor) in patients with or without hepatitis B or C who have progressed on sorafenib is currently ongoing.[65]

Codrituzumab is a humanized monoclonal antibody against glypican-3, expressed in HCC and involved in antibody-dependent cytotoxicity. A randomized second-line placebo-controlled phase 2 trial did not show clinical benefit (PFS 2.6 vs 1.5 months, OS 8.7 vs 10 months).[66]

Pexa-Vec is an oncolytic and immunotherapeutic vaccinia virus designed to selectively replicate in and destroy cancer cells via direct oncolysis with tumor vascular disruption and antitumor immunity. Preclinical and clinical data suggested complimentary effects when combined with sorafenib, and a current phase 3 trial comparing Pexa-Vec + sorafenib to sorafenib alone is currently ongoing. A prior randomized phase 2 trial had shown acceptable safety profile with OS benefit.[67]

Future Directions

While many different treatment regimens have been attempted in HCC, few options have shown significant improvement in outcomes. As in other malignancies, treatment is shifting away from more toxic chemotherapies toward targeted therapy and immunotherapy, although these have also had limited efficacy in HCC. To date, sorafenib remains the only approved systemic treatment available. Future directions are focused on molecular-targeted therapies, especially those with potential biomarkers that may predict or correlate with tumor response.

Several studies have looked at potential biomarkers to determine who will derive benefit from therapy, specifically sorafenib. The response rate with sorafenib is generally low (0.7%-3%), but a small number of cases have demonstrated substantial tumor regression. A study looking at these "responders" found amplication of FGF3 and FGF4, poorly differentiated histology, and multiple lung metastases in 3 of 10 evaluable samples.[68] Longer OS is associated with low baseline AFP, low CP score, compensated cirrhosis, and low baseline ALT. Child Pugh score and baseline AST are also independent prognostic factors.[69] An analysis of the SHARP trial looked at 10 biomarkers measured at baseline and after 12 weeks of treatment and showed that baseline angiopoietin 2 and VEGF concentrations independently predicted survival. ECOG PFS, baseline AFP, and AP also predicted survival. Although none of the biomarkers tested predicted response to sorafenib, patients with high s-c-KIT or low baseline hepatocyte growth factor concentration in the sorafenib cohort showed a trend towards enhanced benefit.[69,70] The ALICE-1 study looked at VEGF and VEGFR genotyping to predict outcomes with sorafenib and identified several polymorphisms (single nucleotide polymorphism [SNPs]) of VEGF that influenced PFS and OS.[71] The ALICE-2 study also showed SNPs of hypoxia-inducible factor-1α (HIF-1α) to be significant for PFS and OS.

Other studies have focused on alternative molecular pathways with potential associated biomarkers. Newer molecular therapies have targeted MEK, MET, and MYC. A study looking at expression of mcl-1, pERK½ and pAKT, MYC, and MET in pretreatment specimens of 44 patients with advanced HCC showed poorer OS with pERK expression and mcl-1 expression; however, this did not correlate with TTP.[70] A study to look at the prognostic and predictive role of eNOS, Ang2, HIF-1, VEGF, and VEGFR polymorphisms as they pertain to PFS in HCC is currently ongoing and expected to be completed in January 2019. A randomized controlled phase 3 study of tivantinib, an MET inhibitor, in patients with HCC who have failed one line of systemic therapy was currently ongoing and was completed in December 2016 A similar phase 3 randomized, double-blinded study of tivantinib in MET-diagnostic high HCC is also ongoing and expected to complete accrual in March 2017.

Epigenetic modifications have been suggested to drive progression to HCC and include DNA methyltransferases and microRNAs (miRNAs). Histone deacetylase (HDAC) inhibitors act to induce cell growth arrest and apoptosis and have been suggested to have activity in HCC. Preclinical models of a pan-HDAC inhibitor MPT0G009 showed increased apoptotic populations and decreased levels of antiapoptotic proteins, suggesting that it could possibly be a potential HCC therapy.[72] A multicenter phase 1/2 study of belinostat in patients with unresectable HCC showed a median PFS of 2.64 months and OS of 6.6 months, which is still inferior to sorafenib; however, HR23B expression was also evaluated as a potential biomarker and was found to be associated with disease stabilization.[73] Vorinostat is another HDAC inhibitor that was found to induce NF-kB in vitro, which may actually lead to cancer cell progression. Studies looking at the combination of sorafenib and vorinostat, where sorafenib would act to enhance the cytotoxicity and inhibit NF-κB activity, showed increased efficacy in vitro and in vivo, suggesting another potential new therapy.[74] A phase 1 trial of sorafenib and vorinostat in advanced HCC is currently ongoing. MicroRNAs are produced by human cells, released in the blood, and thought to play a role in gene expression and cell proliferation. MicroRNAs have a known role in the pathogenesis of HCC; however, it is unknown whether they can be used as markers for diagnosis and survival. Studies are ongoing to determine the presence of miRNAs in patients with HCC and whether there is a correlation between miRNAs in tumor tissue and blood.[75]

Immunotherapy has shown promising results in HCC based on small studies as mentioned above. Currently, we are awaiting the results of phase 3 studies to see whether there is benefit of immunotherapy. In addition to check point inhibitors, there are attempts to use vaccines to treat HCC as well. Preliminary data of a phase 2 study of hepcortespenlisimut-L, an oral vaccine made of tumor antigens and pooled alloantigens, showed decreased AFP levels after 2 months of treatment, which correlated with tumor regression or clearance on computed tomography scans. After 10 months, 93.3% of patients were still alive, with 1 patient 57 months out with no evidence of disease.[76] This study will be completed in December 2019. A phase 3 randomized, placebo-controlled trial is also currently recruiting. As discussed above, it is suspected that checkpoint inhibition may be enhanced by tumor ablative therapies and there are currently ongoing phase 1/2 trials combining these modalities—these are expected to be completed in 2021.

Further molecular profiling may continue to reveal future drug targets and corresponding biomarkers. Given the heterogeneity of HCC, evaluation of those subsets of patients who respond well to certain therapies may also elucidate potential biomarkers and molecular markers that can more effectively guide treatment recommendations.

Authors' Note

The remaining authors report no significant relationship with the companies/organizations whose products or services may be referenced in this article.

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
2. Volk ML, Marrero JA. Early detection of liver cancer: diagnosis and management. *Curr Gastroenterol Rep*. 2008;10(1):60-66.
3. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19(3):329-338.
4. Yu SJ. A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010-2016. *Clin Mol Hepatol*. 2016;22(1):7-17.
5. Caruso ML, Valentini AM. Overexpression of p53 in a large series of patients with hepatocellular carcinoma: a clinicopathological correlation. *Anticancer Res*. 1999;19(5B):3853-3856.
6. Huang CC, Wu MC, Xu GW, et al. Overexpression of the MDR1 gene and P-glycoprotein in human hepatocellular carcinoma. *J Natl Cancer Inst*. 1992;84(4):262-264.
7. Soini Y, Virkajarvi N, Raunio H, et al. Expression of P-glycoprotein in hepatocellular carcinoma: a potential marker of prognosis. *J Clin Pathol*. 1996;49(6):470-473.
8. Nagahama H, Okada S, Okusaka T, et al. Predictive factors for tumor response to systemic chemotherapy in patients with hepatocellular carcinoma. *Jpn J Clin Oncol*. 1997;27(5):321-324.
9. Ikeda M, Okusaka T, Ueno H, et al. Predictive factors of outcome and tumor response to systemic chemotherapy in patients with metastatic hepatocellular carcinoma. *Jpn J Clin Oncol*. 2008;38(10):675-682.
10. Olweny CL, Toya T, Katongole-Mbidde E, et al. Treatment of hepatocellular carcinoma with adriamycin. Preliminary communication. *Cancer*. 1975;36(4):1250-1257.
11. Lai CL, Wu PC, Chan GC, et al. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. *Cancer*. 1988;62(3):479-483.
12. Cheng AL, Yeh KH, Fine RL, et al. Biochemical modulation of doxorubicin by high-dose tamoxifen in the treatment of advanced hepatocellular carcinoma. *Hepatogastroenterology*. 1998;45(24):1955-1960.
13. Porta C, Moroni M, Nastasi G, et al. 5-Fluorouracil and d, l-leucovorin calcium are active to treat unresectable hepatocellular carcinoma patients: preliminary results of a phase II study. *Oncology*. 1995;52(6):487-491.
14. Patt YZ, Hassan MM, Aguayo A, et al. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. *Cancer*. 2004;101(3):578-586.
15. Brandi G, de Rosa F, Agostini V, et al. Metronomic capecitabine in advanced hepatocellular carcinoma patients: a phase II study. *Oncologist*. 2013;18(12):1256-1257.
16. Abdel-Rahman O, Abdel-Wahab M, Shaker M, et al. Sorafenib versus capecitabine in the management of advanced hepatocellular carcinoma. *Med Oncol*. 2013;30(3):655.
17. Yang TS, Lin YC, Chen JS, et al. Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer*. 2000;89(4):750-756.
18. O'Reilly EM, Stuart KE, Sanz-Altamira PM, et al. A phase II study of irinotecan in patients with advanced hepatocellular carcinoma. *Cancer*. 2001;91(1):101-105.
19. Lee J, Park JO, Kim WS, et al. Phase II study of doxorubicin and cisplatin in patients with metastatic hepatocellular carcinoma. *Cancer Chemother Pharmacol*. 2004;54(5):385-390.
20. Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol*. 2013;31(28):3501-3508.
21. Parikh PM, Fuloria J, Babu G, et al. A phase II study of gemcitabine and cisplatin in patients with advanced hepatocellular carcinoma. *Trop Gastroenterol*. 2005;26(3):115-118.
22. Louafi S, Boige V, Ducreux M, et al. Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC): results of a phase II study. *Cancer*. 2007;109(7):1384-1390.
23. Zhu AX, Blaszkowsky LS, Ryan DP, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2006;24(12):1898-1903.
24. Leung TW, Patt YZ, Lau WY, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. *Clin Cancer Res*. 1999;5(7):1676-1681.
25. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst*. 2005;97(20):1532-1538.
26. Kaseb AO, Shindoh J, Patt YZ, et al. Modified cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in

patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. *Cancer*. 2013;119(18):3334-3342.
27. Llovet JM, Villanueva A, Lachenmayer A, et al. Advances in targeted therapies for hepatocellular carcinoma in the genomic era. *Nat Rev Clin Oncol*. 2015;12(8):436.
28. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008; 359(4):378-390.
29. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25-34.
30. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol*. 2012;57(4):821-829.
31. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2006;24(26):4293-4300.
32. Lencioni R, Kudo M, Ye SL, et al. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. *Int J Clin Pract*. 2014;68(5):609-617.
33. Pinter M, Sieghart W, Graziadei I, et al. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. *Oncologist*. 2009;14(1):70-76.
34. Abou-Alfa GK, Johnson P, Knox JJ, et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA*. 2010;304(19): 2154-2160.
35. Zhu AX, Rosmorduc O, Evans TR, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2015;33(6):559-566.
36. Siegel AB, Cohen EI, Ocean A, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol*. 2008;26(18):2992-2998.
37. Kaseb AO, Garrett-Mayer E, Morris JS, et al. Efficacy of bevacizumab plus erlotinib for advanced hepatocellular carcinoma and predictors of outcome: final results of a phase II trial. *Oncology*. 2012;82(2):67-74.
38. Philip PA, Mahoney MR, Holen KD, et al. Phase 2 study of bevacizumab plus erlotinib in patients with advanced hepatocellular cancer. *Cancer*. 2012;118(9):2424-2430.
39. National Institue of Health. A phase II trial of erlotinib plus bevacizumab in advanced hepatocellular carcinoma as a second-line therapy in patients who have received first-line sorafenib therapy (AVF4572). ClinicalTrials.gov Identifier: NCT01180959. 2016.
40. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol*. 2013;31(32):4067-4075.
41. Kang YK, Yau T, Park JW, et al. Randomized phase II study of axitinib versus placebo plus best supportive care in second-line treatment of advanced hepatocellular carcinoma. *Ann Oncol*. 2015;26(12):2457-2463.
42. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16(7):859-870.
43. Cainap C, Qin S, Huang WT, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2015;33(2): 172-179.
44. Bruix J, Tak WY, Gasbarrini A, et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. *Eur J Cancer*. 2013;49(16):3412-3419.
45. Zhang J, Zong Y, Xu GZ, et al. Erlotinib for advanced hepatocellular carcinoma. A systematic review of phase II/III clinical trials. *Saudi Med J*. 2016;37(11):1184-1190.
46. Asnacios A, Fartoux L, Romano O, et al. Gemcitabine plus oxaliplatin (GEMOX) combined with cetuximab in patients with progressive advanced stage hepatocellular carcinoma. *Cancer*. 2008; 112(12):2733-2739.
47. Sanoff HK, Bernard S, Goldberg RM, et al. Phase II study of capecitabine, oxaliplatin, and cetuximab for advanced hepatocellular carcinoma. *Gastrointest Cancer Res*. 2011;4(3):78-83.
48. National Institue of Health. Oxaliplatin, capecitabine, and cetuximab in treating patients with advanced liver cancer (NRR). ClinicalTrials.gov Identifier: NCT00483405. 2016.
49. Chuma M, Terashita K, Sakamoto N. New molecularly targeted therapies against advanced hepatocellular carcinoma: from molecular pathogenesis to clinical trials and future directions. *Hepatol Res*. 2015;45(10):E1-E11.
50. Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol*. 2013;31(28):3517-3524.
51. Llovet JM, Decaens T, Raoul JL, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol*. 2013;31(28):3509-3516.
52. Cheng AL, Thongprasert S, Lim HY, et al. Randomized, open-label phase 2 study comparing frontline dovitinib versus sorafenib in patients with advanced hepatocellular carcinoma. *Hepatology*. 2016;64(3):774-784.
53. Huynh H, Nguyen TT, Chow KH, Tan PH, Soo KC, Tran E. Over-expression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: its role in tumor progression and apoptosis. *BMC Gastroenterol*. 2003;3:19.
54. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol*. 2013;14(1): 55-63.
55. National Institue of Health. Study of tivantinib in subjects with inoperable hepatocellular carcinoma who have been treated with one prior therapy (METIV-HCC). *ClinicalTrials.gov Identifier: NCT01755767*. 2016.
56. Cohn AL, Kelley RK, Yang TS, et al. Activity of cabozantinib (XL184) in hepatocellular carcinoma patients (pts): results from a

phase II randomized discontinuation trial (RDT). *J Clin Oncol*. 2012;30(suppl 4):261-261.
57. National Institue of Health. Study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL). ClinicalTrials.gov Identifier: NCT01908426. 2016.
58. Gao Q, Qiu SJ, Fan J, et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. *J Clin Oncol*. 2007;25(18):2586-2593.
59. Lai CL, Wu PC, Lok AS, et al. Recombinant alpha 2 interferon is superior to doxorubicin for inoperable hepatocellular carcinoma: a prospective randomised trial. *Br J Cancer*. 1989; 60(6):928-933.
60. El-Khoueiry AB, Melero I, Crocenzi TS, et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular. *J Clin Oncol*. 2015;33(suppl 18):LBA101. Abstract.
61. Bruno Sangro IM, Thomas CY, Chiun H, et al. Safety and antitumor activity of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (HCC): Interim analysis of dose-expansion cohorts from the phase 1/2 CheckMate-040 study. *J Clin Oncol*. 2016;34(suppl 15):4078. Abstract.
62. El-Khoueiry AB, Sangro B, Yau TC, et al. Phase I/II safety and antitumor activity of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (HCC): interim analysis of the CheckMate-040 dose escalation study. *J Clin Oncol*. 2016; 34(suppl 15):abstr 4012.
63. Zhu AX, Knox JJ, Kudo M, et al. KEYNOTE-224: phase II study of pembrolizumab in patients with previously treated advanced hepatocellular carcinoma. *J Clin Oncol*. 2017;35(suppl 4S): abstract TPS504.
64. Finn RS, Chan SL, Zhu AX, et al. KEYNOTE-240: Randomized phase III study of pembrolizumab versus best supportive care for second-line advanced hepatocellular carcinoma. *J Clin Oncol*. 2017;35(suppl 4S): abstract TPS503.
65. Abou-Alfa GK, Sangro B, Morse M, et al. Phase 1/2 study of durvalumab and tremelimumab as monotherapy and in combination in patients with unresectable hepatocellular carcinoma (HCC). Paper presented at: ASCO Annual Meeting Proceedings; 2016.
66. Abou-Alfa GK, Puig O, Daniele B, et al. Randomized phase II placebo controlled study of codrituzumab in previously treated patients with advanced hepatocellular carcinoma. *J Hepatol*. 2016;65(2):289-295.
67. Abou-Alfa GK, Galle PR, Chao Y, et al. PHOCUS: a phase 3 randomized, open-label study comparing the oncolytic immunotherapy Pexa-Vec followed by sorafenib (SOR) vs SOR in patients with advanced hepatocellular carcinoma (HCC) without prior systemic therapy. Paper presented at: ASCO Annual Meeting Proceedings; 2016.
68. Arao T, Ueshima K, Matsumoto K, et al. FGF3/FGF4 amplification and multiple lung metastases in responders to sorafenib in hepatocellular carcinoma. *Hepatology*. 2013;57(4):1407-1415.
69. Pinter M, Sieghart W, Hucke F, et al. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. *Aliment Pharmacol Ther*. 2011;34(8):949-959.
70. Llovet JM, Pena CE, Lathia CD, et al. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin Cancer Res*. 2012;18(8):2290-2300.
71. Scartozzi M, Faloppi L, Svegliati Baroni G, et al. VEGF and VEGFR genotyping in the prediction of clinical outcome for HCC patients receiving sorafenib: the ALICE-1 study. *Int J Cancer*. 2014;135(5):1247-1256.
72. Chen MC, Huang HH, Lai CY, et al. Novel histone deacetylase inhibitor MPT0G009 induces cell apoptosis and synergistic anticancer activity with tumor necrosis factor-related apoptosis-inducing ligand against human hepatocellular carcinoma. *Oncotarget*. 2016;7(1):402-417.
73. Yeo W, Chung HC, Chan SL, et al. Epigenetic therapy using belinostat for patients with unresectable hepatocellular carcinoma: a multicenter phase I/II study with biomarker and pharmacokinetic analysis of tumors from patients in the Mayo Phase II Consortium and the Cancer Therapeutics Research Group. *J Clin Oncol*. 2012;30(27):3361-3367.
74. Hsu FT, Liu YC, Chiang IT, et al. Sorafenib increases efficacy of vorinostat against human hepatocellular carcinoma through transduction inhibition of vorinostat-induced ERK/NF-kappaB signaling. *Int J Oncol*. 2014;45(1):177-188.
75. Qi J, Wang J, Katayama H, et al. Circulating microRNAs (cmiRNAs) as novel potential biomarkers for hepatocellular carcinoma. *Neoplasma*. 2013;60(2):135-142.
76. Tarakanovskaya MG, Chinburen J, Purevsuren G, et al. Immunotherapy of liver cancer with hepcortespenlisimut-L: open-label phase II clinical study in patients with advanced HCC. *J Immunother Cancer*. 2015;3(suppl 2):P200.
77. Ikeda M, Okusaka T, Ueno H, et al. A phase II trial of continuous infusion of 5-fluorouracil, mitoxantrone, and cisplatin for metastatic hepatocellular carcinoma. *Cancer*. 2005;103(4):756-762.
78. Boucher E, Corbinais S, Brissot P, et al. Treatment of hepatocellular carcinoma (HCC) with systemic chemotherapy combining epirubicin, cisplatinum and infusional 5-fluorouracil (ECF regimen). *Cancer Chemother Pharmacol*. 2002;50(4):305-308.
79. Tanioka H, Tsuji A, Morita S, et al. Combination chemotherapy with continuous 5-fluorouracil and low-dose cisplatin infusion for advanced hepatocellular carcinoma. *Anticancer Res*. 2003; 23(2C):1891-1897.
80. Boige V, Raoul JL, Pignon JP, et al. Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. *Br J Cancer*. 2007; 97(7):862-867.