

Hepatocellular carcinoma (HCC): beyond sorafenib – chemotherapy

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary liver cancer with poor prognosis. The incidence of HCC and HCC-related deaths have increased over the last several decades. However, the treatment options for advanced HCC are very limited. Sorafenib remains the only drug approved for systemic treatment for advanced HCC. However, prior to sorafenib era conventional cytotoxic chemotherapies have been studied in advanced HCC. In this review, clinical studies of systemic chemotherapy for advanced HCC will be summarized and discussed.

Keywords: Advanced HCC; chemotherapy

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. HCC is the sixth most common cancer and the second leading cause of cancer-related deaths worldwide (1). In contrast to most solid cancers, the incidence of HCC and HCC-related deaths have increased over the last several decades in many parts of the world including United States. In the United States, more than 39,230 new cases of HCC and more than 27,170 HCC-related deaths were predicted in 2016 (2). The prognosis of HCC is dismal with a 3-year survival rate of 12.7% and a median survival of 9 months (3).

HCC can be treated with surgical resection, liver transplantation, liver directed therapy and systemic therapy. Among these options, only surgical resection and liver transplantation are considered as potentially curative approaches. However, only 15% patients are eligible for the potentially curative treatments (4) since a majority of patients will present with advanced disease. In 2016, sorafenib is still the only FDA approved systemic therapy for advanced HCC. In contrast to other solid cancer, systemic chemotherapy has not been used routinely since

HCC is considered as a chemotherapy resistant tumor with overexpression of dihydropyrimidine dehydrogenase, the P-glycoprotein gene product and the multidrug resistance gene, *MDR-1* (5-7). Furthermore, patients with advanced HCC usually have significant underlying liver disease which is associated with poor tolerability to systemic chemotherapy. However, there have been many trials evaluating systemic chemotherapy in patients with advanced HCC prior to sorafenib era. In this paper, we will attempt to concisely summarize the historical perspective and the current status of systemic therapy development in HCC. The role of targeted therapy in HCC will not be covered in this review paper.

Chemotherapy

Single agent chemotherapy

Doxorubicin

Prior to the approval of sorafenib, doxorubicin was commonly used in the treatment of advanced HCC. An initial phase II study of single agent doxorubicin demonstrated 79% (11/14) objective response rates

Table 1 Phase II and III studies of single agent systemic chemotherapy in hepatocellular carcinoma

Regimen	N	Treatment setting	Primary endpoint	HR (95% CI)	P value	Reference
Doxorubicin	14	First line systemic	ORR: 78.6%	NA	NA	(8)
Doxorubicin vs. nolatrexed	223 vs. 222	Not restricted	OS, median (weeks): 32.3 vs. 22.3	0.75	0.0068	(9)
Doxorubicin vs. PIAF	94 vs. 94	First line systemic	OS, median, (months): 6.83 vs. 8.67	0.97 (0.71–1.32)	0.8300	(10)
Doxorubicin vs. 5-FU, methotrexate, cyclophosphamide and vincristine	47 vs. 19	Not documented	ORR: 24% vs. 0%	NA	<0.0500	(11)
Doxorubicin vs. etoposide	28 vs. 22	Not restricted	ORR: 28% vs. 18%	NA	NS	(12)
5-FU plus leucovorin	25	Not documented	ORR: 28%	NA	NA	(13)
	15	Not documented	ORR: 7%	NA	NA	(14)
Capecitabine (first line) vs. capecitabine (sorafenib refractory)	59 vs. 31	First line systemic sorafenib refractory	PFS, median (months): 6.03 vs. 3.27	NA	NA	(15)
Sorafenib vs. capecitabine	26 vs. 26	First line systemic	PFS, median, (months): 6 vs. 4	2.71 (1.34–5.43)	0.0050	(16)
Gemcitabine	28	First line systemic	ORR: 17.8%	NA	NA	(17)
	30	1st/2nd line systemic	ORR: 0%	NA	NA	(18)
	20	Not documented	ORR: 5%	NA	NA	(19)
Irinotecan	14	1st/2nd line systemic	ORR: 7%	NA	NA	(20)
	29	First line systemic	ORR: 0%	NA	NA	(21)

CI, confidence interval; HR, hazard ratio; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; 5-FU, 5-fluorouracil; NS, not significant.

including three complete responses in advanced HCC (Table 1) (8). However, subsequent studies demonstrated only limited efficacy (<20% clinical responses) without significant survival benefit (9-12,22). The reason for disparate outcome is unclear but patient selection in earlier trials may have contributed to better outcome. Furthermore acute and accumulative toxicity such as cardiotoxicity, limited adequate dosing of this compound as well. Absence of proven efficacy and toxicity explains why doxorubicin is not an approved HCC treatment and this is why it was not used for the control arm in the sorafenib trials.

To overcome the shortcomings of doxorubicin pegylated liposomal doxorubicin (PLD) was developed to improve anti-tumor activity and to reduce toxicity. PLD is a liposomal formulation of doxorubicin which reduces uptake by the reticulo-endothelial system. This formulation allows an extended circulation time and a reduces volume of distribution, thereby promoting tumor uptake with reduced cardiotoxicity (23). The efficacy of PLD was evaluated

in several phase II trials in patients with advanced HCC. Although a favorable toxicity profile has been observed, the studies failed to show meaningful clinical outcome (24-27). The reduced uptake of PLD in organs including liver may be responsible for the lack of efficacy. Therefore PLD as a single agent has no significant activity against advanced HCC despite better toxicity profile.

5-fluorouracil (5-FU)

5-FU which is commonly been used in the treatment of colorectal cancer has been evaluated for advanced HCC as well. A phase II study of 5-FU combined with leucovorin showed modest activity with 28% response rates in advanced HCC (13). However, another phase II study of 5-FU with leucovorin showed poor clinical response with only 1 partial response (7%) (14).

Capecitabine which is an orally active form of fluoropyrimidine demonstrated no clinically significant

influence on the pharmacokinetics in patients with mildly to moderately impaired hepatic function (28). Therefore, capecitabine has been evaluated in patients with advanced HCC which is generally associated with impaired hepatic function. In a phase II study, 59 treatment-naïve patients and 31 sorafenib refractory patients with advanced HCC were treated with metronomic capecitabine (15). A median progression-free survival (PFS) and overall survival (OS) of previously untreated patients were 6.0 and 14.5 months with response rates of 5%, and those of sorafenib refractory patients were 3.3 and 9.8 months, respectively with no objective responses. Interestingly, metronomic capecitabine treatment prolonged OS of the treatment-naïve patients cohort compared with matched historical controls (median OS: 15.6 *vs.* 8.0 months, $P=0.043$) in the trial. However, the survival benefit from capecitabine should be interpreted cautiously since the trial was not a randomized study.

Recently, a small randomized phase II study comparing sorafenib *vs.* capecitabine was conducted in patients with advanced HCC (16). The primary objective of this study was PFS. Unfortunately, capecitabine showed significant inferiority to sorafenib in terms of PFS (median PFS: 4 *vs.* 6 months, $P<0.005$) and OS (median OS: 5 *vs.* 7 months, $P<0.016$). Due to the lack of large randomized controlled studies, the antitumor activity of single agent 5-FU or capecitabine is unknown.

Gemcitabine

In contrast to other chemotherapeutic agents, gemcitabine is not subjected to the chemotherapy resistance mechanisms of HCC such as overexpression of dihydropyrimidine dehydrogenase, the P-glycoprotein or the MDR-1 protein (5-7). In several pre-clinical studies gemcitabine demonstrated strong antitumor effects on HCC (29-31). Therefore, based on pre-clinical rationale gemcitabine was evaluated in patients with advanced HCC. In a phase II study of gemcitabine in treatment-naïve patients with advanced HCC, 5 patients (18%) had objective responses with mild toxicities (17). However, two subsequent phase II studies of gemcitabine failed to show meaningful clinical efficacy [0-5% overall response rate (ORR)] (18,19). The disparate outcomes may come from differences between Asian and Western patient population and the etiology of HCC.

Irinotecan

Irinotecan, a topoisomerase-1 inhibitor, has broad spectrum of antitumor activity in multiple malignancies. The active metabolite, SN-38 undergoes enterohepatic recirculation

which leads to high local concentrations in the hepatobiliary tree (32). Based on these characteristics of irinotecan, irinotecan was evaluated in phase II studies in patients with advanced HCC. Unfortunately, antitumor activity of single agent irinotecan was not significant with objective response rates of only 0-7% (20,21).

Combination chemotherapy

Doxorubicin based combination chemotherapy

Several doxorubicin based combination regimens were evaluated in advanced HCC to enhance antitumor activity (Table 2). A phase II study of doxorubicin plus cisplatin resulted in marginal clinical benefit including the objective response rates of 18.9% (7/37), the median OS of 7.3 months and the median PFS of 6.6 months with tolerable adverse effects (33).

Adding capecitabine to doxorubicin and cisplatin also showed modest antitumor activity including 7 partial responses (24%) with the median PFS and median OS of 3.7 and 7.7 months, respectively (34).

While these doxorubicin based combination regimens showed only modest antitumor activity, the PIAF regimen, another doxorubicin based combination, demonstrated promising results. PIAF is an active and toxic combination chemotherapy regimen consisting of cisplatin, interferon α , doxorubicin and 5-FU. An initial phase II study of the PIAF regimen reported a relatively high objective response rate up to 26% (13/50) (35). Furthermore, 4 of 9 patients who underwent surgical resection after achieving partial response had complete pathological response with no viable tumor cells. The promising results from the phase II study led to a larger phase III study. Although the high response rate of the PIAF regimen was once again confirmed in a randomized phase III study comparing PIAF with doxorubicin (20.9% *vs.* 10.5%), there was no survival benefit (median OS: 8.7 *vs.* 6.8 months, $P=0.83$) with significant treatment-related grade 3/4 toxicities including neutropenia, thrombocytopenia and anemia (10). The failure to show a survival benefit despite the higher response rate might be explained by lack of patient selection in the study. The importance of patient selection for the PIAF regimen was confirmed by several retrospective studies. One retrospective study demonstrated that when the HCC patients with normal total bilirubin and non-cirrhotic livers were selected out, the ORRs were much higher (50.0% *vs.* 6.3%, $P=0.004$) compared with patients with abnormal bilirubin and liver cirrhosis (46). In another retrospective

Table 2 Phase II and III studies of combination systemic chemotherapy in hepatocellular carcinoma

Regimen	N	Treatment setting	Primary endpoint	HR (95% CI)	P value	Reference
Capecitabine; capecitabine plus streptozotocin; capecitabine plus methyl-CCNU; doxorubicin	43; 33; 44; 36	First line systemic	ORR: 0%; 12%; 5%; 10%	NA	NA	(22)
Doxorubicin plus cisplatin	37	First line systemic	ORR: 18.9%	NA	NA	(33)
Doxorubicin, cisplatin and capecitabine	29	First line systemic	ORR: 24%	NA	NA	(34)
PIAF	50	Not restricted	ORR: 26%	NA	NA	(35)
5-FU, mitoxantrone and cisplatin	50	First line systemic	ORR: 27%	NA	NA	(36)
Epirubicin, cisplatin and 5-FU (ECF)	21	First line systemic	ORR: 14.5%	NA	NA	(37)
Capecitabine plus cisplatin	32	First line systemic	ORR: 6.3%	NA	NA	(38)
FOLFOX vs. doxorubicin	184 vs. 187	Not restricted	OS, median (months): 6.40 vs. 4.97	0.80 (0.63–1.02)	0.07	(39)
XELOX	50	First line systemic	ORR: 6%	NA	NA	(40)
5-FU plus interferon α	43	Not restricted	ORR: 25%	NA	NA	(41)
Gemcitabine plus cisplatin	30	First line systemic	ORR: 20%	NA	NA	(42)
	15	First line systemic	ORR: 6.7%	NA	NA	(43)
PEG liposomal doxorubicin plus gemcitabine	41	First line systemic	ORR: 24%	NA	NA	(44)
GEMOX	23	Not restricted	ORR: 18%	NA	NA	(45)

CI, confidence interval; HR, hazard ratio; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; 5-FU, 5-fluorouracil; FOLFOX, oxaliplatin, 5-FU and leucovorin; XELOX, capecitabine and oxaliplatin; GEMOX, gemcitabine followed by oxaliplatin.

study from MD Anderson, the authors demonstrated that modified PIAF revealed higher objective response rate (36% *vs.* 15%, $P=0.013$), higher rate of resectability (33% *vs.* 10%, $P=0.004$) and longer median OS (21.3 *vs.* 10.6 months, $P=0.002$) than conventional high dose PIAF in patients with good performance status and without hepatitis or cirrhosis (47). Therefore, PIAF may be a reasonable option for patients with good performance status with normal liver function. However, toxicity of the regimen is a concern.

5-FU based combination chemotherapy

Due to the modest clinical efficacy of 5-FU or capecitabine as a single agent, 5-FU and capecitabine were combined with other chemotherapeutic agents including cisplatin and oxaliplatin. Two phase II studies of 5-FU, cisplatin and mitoxantrone reported objective response rates of 24–27% with median PFS of 2.5–4 months and median OS of 4.9–11.6 months (36,48). Other combination such as epirubicin, cisplatin and 5-FU (ECF) regimen or capecitabine and cisplatin have been evaluated as well. The

combinations tend to have higher response rate but no definite conclusion can be drawn from these studies due to small number of patients (37).

Oxaliplatin, 5-FU and leucovorin (FOLFOX) and capecitabine and oxaliplatin (XELOX) which are commonly used in advanced colorectal cancer were evaluated in advanced HCC. In a randomized phase III study, FOLFOX showed improved ORR (8.2% *vs.* 2.7%, $P=0.02$) and improved PFS (median PFS: 2.9 *vs.* 1.8 months, $P\leq 0.001$) with a non-significant trend for increased OS (median OS: 6.4 *vs.* 5.0 months, $P=0.07$) compared with single agent doxorubicin (38). The most common grade 3 to 4 adverse events from FOLFOX were neutropenia (30.6%), leukocytopenia (8.7%), thrombocytopenia (7.7%) and anemia (4.9%) in the study. However, the interpretation of the trial is difficult as the trial was conducted in Asia where hepatitis B is the underlying causes of liver cirrhosis. Therefore, it is unclear if the results can be duplicated in the western hemisphere where hepatitis C is the number one cause of liver cirrhosis. A single arm phase II study of

XELOX demonstrated better outcome with median PFS of 4.1 months and median OS of 9.3 months (39). However, this was not a randomized study thus limiting any definite conclusion.

5-FU was also evaluated in combination with interferon α which has direct antitumor activity by upregulation of MCH class I molecules on tumor cells, promotion of tumor cell apoptosis and antiangiogenic effects on tumor neovasculature (40) for treatment of advanced HCC. In a phase II study of 5-FU plus interferon α , 9 objective responses (25%) were observed with median OS of 19.5 months (49). However, another study failed to show any clinical efficacy of the combination of 5-FU and interferon α in heavily pretreated patients with advanced HCC (41).

Gemcitabine based combination chemotherapy

To enhance the antitumor activity, gemcitabine was combined with cisplatin. Gemcitabine plus cisplatin demonstrated modest clinical activity (25% objective response rates) with an acceptable toxicity profile in a retrospective study of 24 Indian patients with HCC (50). Similar with the retrospective study, a phase II study of gemcitabine plus cisplatin reported a partial response of 20% and a disease control rate of 63% (objective response plus stable disease) with median PFS of 18 weeks and median OS of 21 weeks in 30 patients with unresectable HCC (51). Observed grade 3 to 4 toxicities were anemia (44%), neutropenia (26%) and thrombocytopenia (14%) in the study. However, another phase II study with reduced dose of gemcitabine plus cisplatin showed poor clinical activity with only 1 partial response in 15 patients and extremely short PFS (median: 6 weeks) and OS (median: 18 weeks) (42). The reason for the poor outcome may be attributed to the fact that more than half of the patients had significant hepatic impairment (Child-Pugh B and C liver cirrhosis), and dose of gemcitabine and cisplatin was much lower than in the other study (42). Since patient selection plays a big role in the clinical outcome of the combination, gemcitabine plus cisplatin can be considered for selected patients who are not eligible for clinical trials and refractory to sorafenib with mild hepatic impairment.

Another gemcitabine based combination chemotherapy, gemcitabine plus PLD treatment induced 10 objective clinical responses (24%) including 3 complete responses with median PFS of 5.8 months and median OS of 22.5 months in a phase II study (43). The results are very promising especially with the significantly improved median OS. However, further randomized studies are needed to confirm the findings.

Gemcitabine followed by oxaliplatin (GEMOX) is an attractive option for patients with advanced HCC since GEMOX has the lack of renal and hepatotoxicity. Although GEMOX was well-tolerable with the most common grade 3/4 toxicities of thrombocytopenia (27%) and neutropenia (24%) in patients with advanced HCC, the clinical outcome was not impressive with ORR of 18% (n=6) in a phase II study (44). Interestingly, all the objective responses were observed in patients with nonalcoholic underlying liver disease (6/21) but not with alcoholic liver disease (0/13).

Hormonal therapy

Previously, expression of estrogen receptors and somatostatin receptors was reported in HCCs (45,52), suggesting potential role of estrogen and somatostatin in HCC. Therefore, hormonal therapy such as tamoxifen, megestrol, octreotide and lanreotide was extensively studied for the treatment of advanced HCC. Initial early phase studies demonstrated modest clinical activity of these agents. However, subsequent randomized trials failed to show antitumor activity of hormonal therapy (53-59). Based on *in vitro* data demonstrating tamoxifen can reverse multidrug resistance in human cancer cells (60), the combination of tamoxifen and chemotherapy such as doxorubicin was investigated in patients with advanced HCC which highly expresses multidrug resistance gene, *MDR-1*. However, tamoxifen plus doxorubicin was not superior to doxorubicin alone in overall clinical response or OS (61). Another phase II study of the combination of tamoxifen and doxorubicin showed 12 partial responses (33.3%), and the median OS of the responders was only 10 months (62).

Interestingly, recent data have revealed that estrogen exerts protective effects against HCC through IL-6 restriction, STAT3 inactivation and tumor associated macrophage inhibition (63), which may explain the lack of efficacy of hormonal therapy in advanced HCC. Currently, hormonal therapy is not recommended for advanced HCC.

Systemic therapy plus targeted therapy

Combination with sorafenib

Since sorafenib was approved for advanced HCC, multiple therapeutic agents targeting vascular endothelial growth factor (VEGF) and/or epidermal growth factor receptor (EGFR) pathway have been studied. Since studies with

Table 3 Phase II and III studies of combination of systemic chemotherapy plus targeted therapy in hepatocellular carcinoma

Regimen	N	Treatment setting	Primary endpoint	HR (95% CI)	P value	Reference
Doxorubicin plus tamoxifen	38	First line systemic	ORR: 33.3%	NA	NA	(63)
Doxorubicin plus sorafenib vs. doxorubicin	47 vs. 49	First line systemic	Time to progression, median (months): 6.4 vs. 2.8	0.50 (0.30–0.90)	0.02	(64)
Doxorubicin plus sorafenib vs. sorafenib	173 vs. 173	First line systemic	OS, median (months): 9.3 vs. 10.5	1.06 (0.80–1.40)	NS	(65)
Bevacizumab plus GEMOX	33	First line systemic	ORR: 20%	NA	NA	(66)
Bevacizumab plus capecitabine	45	First line systemic	ORR: 9%	NA	NA	(67)
Bevacizumab plus XELOX	40	First line systemic	PFS, median (months): 6.8	NA	NA	(68)
Cetuximab plus GEMOX	44	First line systemic	ORR: 20%	NA	NA	(69)

CI, confidence interval; HR, hazard ratio; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; XELOX, capecitabine and oxaliplatin; GEMOX, gemcitabine followed by oxaliplatin; NS, not significant.

the targeted agents including sorafenib are covered in accompanying reviews, we will discuss the combination of chemotherapy with targeted therapy (*Table 3*). To enhance anticancer activity of sorafenib, the combination of sorafenib and doxorubicin was evaluated in several studies. Sorafenib plus doxorubicin is an attractive regimen since inhibition of Ras/Raf/MEK/ERK signaling pathway by sorafenib may suppress expression of MDR-1 (70). Therefore, the combination can increase area under the curve (AUC) of doxorubicin without worsening toxicities (71). In a double-blind phase II study, sorafenib plus doxorubicin resulted in prolonged PFS (median PFS: 6.0 vs. 2.7 months, $P=0.006$) and OS (median OS: 13.7 vs. 6.5 months, $P=0.006$) compared with doxorubicin monotherapy (72). Based on the promising results of the phase II study, Cancer and Leukemia Group B (CALGB) conducted a phase III trial randomizing sorafenib plus doxorubicin compared to sorafenib alone. However, the preliminary report presented in 2016 demonstrated that the combination of sorafenib and doxorubicin was associated with shorter OS (median OS: 9.3 vs. 10.5 months) and higher toxicities than single agent sorafenib (64).

Combination with bevacizumab

HCC is a hypervascular tumor, and neovascularization plays an important role in the growth and progression of HCC (65). Targeting angiogenesis in HCC has been studied, and bevacizumab, a monoclonal antibody against VEGF-A showed modest antitumor activity in advanced HCC (73).

Bevacizumab in combination with chemotherapy such as GEMOX and XELOX were also evaluated in advanced HCC based on the fact that bevacizumab may enhance delivery and tumor uptake of drugs by alteration of tumor vasculature in tumors (74). A phase II study of gemcitabine, oxaliplatin and bevacizumab resulted in 6 objective responders (20%) with median PFS of 5.3 months and median OS of 9.6 months (75). Bevacizumab plus capecitabine as frontline treatment demonstrated modest antitumor activity (4 objective responses: 9%) with median PFS of 2.7 months and median OS of 5.9 months (66). When bevacizumab was combined with XELOX, median PFS and OS was 6.8 and 9.8 months, respectively with 8 partial responses (20%) (67).

Combination with cetuximab

EGFR is expressed on HCC cell lines, and the EGFR pathway has been reported as an essential player in the development of HCC (68). Several studies reported the modest clinical efficacy of erlotinib, an EGFR tyrosine kinase inhibitor in advanced HCC (76). An EGFR inhibitor (cetuximab) combined with chemotherapy was investigated in a phase II study (69). In the study, cetuximab plus GEMOX (gemcitabine and oxaliplatin) resulted in 20% confirmed response rates (9 patients) with median PFS of 4.7 and median OS of 9.5 months. The most common grade 3 to 4 toxicities were thrombocytopenia (24%), neutropenia (20%), cutaneous toxicity (16%) and neurotoxicity (11%). Large randomized trials are needed to confirm the efficacy of the combination regimen.

Conclusions

HCC is one of the increasing major health problems in both developing and developed countries. Unfortunately, only limited systemic treatment options are available for advanced HCC. Most of the trials using systemic chemotherapies were conducted in pre-sorafenib era and it has been difficult to interpret these studies due to small sample sizes, heterogeneous population and lack of randomization. Furthermore, most of the earlier studies did not stratify patients based on the severity of underlying cirrhosis or other factors, making comparison of study results difficult. Therefore, cytotoxic chemotherapy will play a minor role in the treatment of advanced HCC in the era of targeted therapy. Nevertheless, systemic chemotherapies may be considered in certain patients with good liver function test. Regimens such as PIAF can be used if aggressive therapy is desired with the high response rate and regimens including FOLFOX and gemcitabine plus cisplatin can be used in sorafenib refractory patients with good performance status if no clinical trials are available. Single agent such as capecitabine or 5-FU monotherapy can be considered for elderly and frail patients whose tumor is refractory to sorafenib. Finally, understanding the complex molecular biology of HCC with further studies and further evaluation of combination chemotherapy with other therapeutic agents such as molecular targeted therapy and immunotherapy may improve clinical outcome in this resilient tumor.

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Footnote

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