Progression of systemic chemotherapy with oxaliplatin-containing regimens for advanced hepatocellular carcinoma in China

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Hepatocellular carcinoma (HCC) characterized by insidious onset is a highly invasive malignance and has a rapid progress. The majority of patients, especially in Asian countries, present with locally advanced or distant metastatic disease at diagnosis and are not eligible for local treatment. Before the publication of the EACH study results showing the survival benefits of the FOLFOX 4 regimen in Chinese patients with advanced HCC, no chemotherapeutic drug or regimen was considered as systemic chemotherapy standard for this group of patients due to the lack of evidence-based recommendations. Oxaliplatin-containing regimens have shown clinical activity against advanced HCC with an acceptable safety profile. The aim of this article is to present a review of the scientific evidence mainly originating from China that supports the recommendation of oxaliplatin-based regimens for the treatment of Chinese patients with advanced HCC.

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Practice points

- Hepatocellular carcinoma (HCC) is a very common malignant tumor with especially higher incidence and special characters in China; the prognosis of patients with advanced HCC is very poor.
- Systemic chemotherapy has commonly been used in clinical as palliative therapy in patients with advanced HCC but high level of evidence was lack of.
- Oxaliplatin is the third-generation platinum with higher antitumor activity and lower toxicity. Multiple mechanisms of action on HCC have been extensively studied in China.
- Oxaliplatin-containing regimens such as FOLFOX4, XELOX and GEMOX have shown clinical activity with an acceptable safety profile in many clinical studies.
- According to the results of EACH study and subgroup analysis of it, it has been shown that systemic chemotherapy based with oxaliplatin may have a higher objective response and improving survival time for Asian, especially Chinese advanced HCC patients.
- Using oxaliplatin-based regimens in combination with molecular target drug, especially sorafenib, has shown some encouraging results, warrant large-scale, randomized and controlled clinical studies to confirm.
- Oxaliplatin-based regimens have been used as adjuvant therapy following HCC resection or orthotopic liver transplantation in Chinese patients with good results, deserve to further study.

KEYWORDS

• hepatocellular carcinoma
• oxaliplatin • oxaliplatin-based regimens • systemic chemotherapy

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Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors worldwide with an estimated incidence of 782,000 new cases and 746,000 deaths in 2012 [1]. Annually, more than two-thirds of the new cases are diagnosed in the Western Pacific region, with the highest number of new cases coming from China (395,000 cases in 2012) [1]. HCC is a malignancy characterized by insidious onset, highly invasive and rapid progress. Therefore, despite regular screening of patients at high risk for developing HCC, early diagnosis remains a great challenge, and the majority of patients, especially in the Asian countries including China, often presents with locally advanced or distant metastatic disease at diagnosis, thus not being eligible for local treatment such as resection or liver transplantation, local ablation or transcatheter arterial chemoembolization (TACE) [2]. The pathogenesis, clinical features, biological behavior, prognosis and treatment selection in Chinese patients are markedly different from those patients in western countries. In fact, HCC in China and the western world can be seen as two different diseases. Due to delayed diagnosis and limited therapeutic options, the prognosis of those patients with advanced HCC is very poor. When receiving so called best supportive care (BSC), the mean survival of those patients is 6–9 months in western countries and only 3–5 months in Asian countries (excluding Japan) [3,4]. Although the molecular targeted drug sorafenib has been approved for the treatment of advanced HCC, the very low response rate (RR), relatively limited survival benefit, no obvious improvement of main symptoms, relatively high toxicity and high cost do limit its wide use in clinical practice in China [5].

HCC was considered as resistant to common cytotoxic drugs [6], but systemic chemotherapy has been used as palliative therapy in patients with advanced HCC for several decades [5]. Before the publication of the EACH study results, no chemotherapeutic drug or regimen was considered as standard of care for advanced HCC patients due to the lack of evidence-based recommendations. Positive results of oxaliplatin-based regimens in several Phase I–II clinical trials enrolling patients with advanced HCC [7–11], have opened the door for larger Phase III clinical trials investigating the efficacy of oxaliplatin either alone or in combination with other chemotherapeutic agents or new molecular targeted drugs [12]. The publication

of the final results of the EACH study was an important milestone in the treatment of Asian patients with advanced HCC [12]. Following this, systemic chemotherapy with the FOLFOX4 regimen was accepted and included in the Experts Consensus of Standard Diagnosis and Treatment on Primary Liver Cancer formulated by the Chinese Medical Association, Chinese Society of Liver Cancer, Chinese Anti-cancer Association and Chinese Society of Clinical Oncology, and also in the Clinical Guideline for Diagnosis and Treatment of Primary Liver Cancer published by the National Health and Family Planning Commission of the People's Republic of China. Additionally, the China Food and Drug Administration (CFDA) has approved advanced HCC as a new indication of oxaliplatin use in 2013 [5]. The aim of this article is to present a review of the scientific evidence, mainly originating from China, which supports the recommendation of oxaliplatin-based regimens for the treatment of Chinese patients with advanced HCC.

Oxaliplatin – mechanism of action

Oxaliplatin is the third-generation platinum featuring the 1,2-diaminocyclohexane carrier ligand [13]. Oxaliplatin has been shown to have antitumor activity both *in vivo* and *in vitro* without crossreactivity with cisplatin and carboplatin. Therefore, it has proven to be a good alternative therapy in gastrointestinal cancers that are usually resistant to cisplatin and carboplatin [14]. Due to relatively positive results in clinical trials enrolling Chinese patients with HCC, the mechanism of action of oxaliplatin has been extensively studied in China.

Multiple mechanisms of action have been postulated through which oxaliplatin may promote cancer cell apoptosis. Inhibition of tumor cell proliferation is exerted through DNA lesion, inhibition of DNA replication and transcription, as well as immunologic mechanisms, that is through initiation of immunological signals on the surface of tumor cells followed by IFN gamma production by T cells and interaction with the toll-like receptor 4 of dendritic cells [15]. It has been also hypothesized that the induction of DNA lesions by oxaliplatin stabilizes the tumor suppression gene *p53* and activates the *p53* signaling pathways (the death receptor pathway and the mitochondrial pathway) which, in turn, results in the inhibition of the cell cycle progression followed by DNA repair

or apoptosis [16,17]. Using cell lines, it has been shown that in response to oxaliplatin *p53* activates the DR5 (the death domain-containing receptor for the TNF-related apoptosis-inducing ligand [TRAIL]) [18], and down-regulates the expression of survivin and BCL-2, thus leading to apoptosis through the activation of the caspase-8 pathway [19]. The exposure of cells to oxaliplatin was also followed by cell cycle arrest in Phase S, through upregulation of *p21* expression, downregulation of cyclin-dependent kinase 4 and cyclin D1, and the amplitude of its effects increased with the dose and time of exposure [20].

Another mechanism through which oxaliplatin was postulated to exert its antitumor effects is the inhibition of HCC cells adhesion, motility and invasion [21,22], probably through downregulation of RhoC expression which has been shown to be associated with the metastatic potential of HCC cells [23]. Furthermore, oxaliplatin involvement in the inhibition of angiogenesis induced by the VEGF? [24], transient decrease of hypoxia [25] and induction of cell autophagy [26] has also been described.

It should be mentioned that except the formation of inter- and intra-strand crosslinks in DNA, other possible mechanisms are supported

by less compelling evidence. But these theoretical mechanisms deserve to further intensive study.

Efficacy & safety of chemotherapy with oxaliplatin-based regimens

In patients with inoperable HCC, systemic chemotherapy has been used as a treatment option before sorafenib became available, but no standard chemotherapy regimen associated with a obvious survival benefit was available in the past. However, oxaliplatin-containing regimens such as FOLFOX4, XELOX and GEMOX have shown clinical activity against advanced HCC with an acceptable safety profile in several Phase II studies [7–11].

• FOLFOX4 regimen (Tables 1 & 2)

The oxaliplatin (eloxatin®) + 5-fluorouracil (5-U)/leucovorin (FOLFOX4) compared with single-agent doxorubicin (adriamycin) as palliative chemotherapy in advanced HCC patients ineligible for curative resection or local treatment (EACH) study, was a landmark trial that has shaped the treatment of Asian patients with advanced HCC, and confirmed that oxaliplatin-based systemic chemotherapy could safely and effectively control the disease and improve survival in these patients [12]. The EACH study

Table 1. Summary of clinical studies with oxaliplatin-based regimens enrolling Chinese patients with advanced hepatocellular carcinoma.

Study (year)	Design	No of patients on oxaliplatin-based regimen	No of patients in the control group	Ref.
Chemotherapy				
Qin S <i>et al.</i>	Open-label, randomized, Phase III	FOLFOX4 = 184	Doxorubicin = 187	[12]
Qin S <i>et al.</i>	Open-label, randomized, Phase III	FOLFOX4 = 140	Doxorubicin = 139	[27]
Yang L <i>et al.</i>	Single-arm	FOLFOX4 = 77	None	[29]
Zhou H <i>et al.</i>	Single-arm	FOLFOX4 = 20	None	[30]
Chen G <i>et al.</i>	Single-arm	H101 plus FOLFOX4 = 22	None	[31]
Yang L <i>et al.</i>	Clinical observation	XELOX = 31	None	[35]
Yin Z <i>et al.</i>	Clinical observation	XELOX = 20	FOLFOX6 = 20	[36]
He SL <i>et al.</i>	Single-arm	CAPEOX = 32	None	[37]
Wang F <i>et al.</i>	Clinical observation	FOLFOX4 = 9 XELOX = 7 patients who had disease progression after sorafenib	None	[40]
Liu S	Single-arm	S-1 plus oxaliplatin = 42	None	[43]
Li S <i>et al.</i>	Single-arm	GEMOX = 40	None	[48]
Yau T <i>et al.</i>	Single-arm, Phase II	SECOX = 51	None	[58]
Zhu AX <i>et al.</i>	Single-arm, Phase II	GEMOX-B = 33	None	[59]
Sun W <i>et al.</i>	Single-arm, Phase II	XELOX plus bevacizumab = 40	None	[60]
Adjuvant chemotherapy				
Chen J <i>et al.</i>	Retrospective analysis	FOLFOX4 = 27	No adjuvant therapy = 88	[69]
Li K <i>et al.</i>	Open-label, randomized	FOLFOX4 = 45	Best supportive care = 44	[70]
Wang L <i>et al.</i>	Open-label, randomized	Oxaliplatin, 5-FU plus calcium formyltetrahydrofolate = 26	None	[72]

Table 2. Efficacy of chemotherapy with oxaliplatin-based regimens in clinical trials enrolling Chinese patients with advanced hepatocellular carcinoma.

Study (Year)	Treatment	DCR (%)	RR (%)	TTP/PFS	Median OS	Ref.
Chemotherapy						
Qin S <i>et al.</i>	FOLFOX4/doxorubicin	52.17	8.15	2.93 months	6.4 months	[12]
Qin S <i>et al.</i>	FOLFOX4/doxorubicin	47.1	8.6	2.4 months	5.7 months	[27]
Yang L <i>et al.</i>	FOLFOX4	55.6	4.2	2.7 months	6.1 months	[29]
Zhou <i>et al.</i>	FOLFOX	60.0	20.0	2.2 months	5.0 months	[30]
Chen G <i>et al.</i>	H101 plus FOLFOX4	60.0	25.0	3.1 months	Not available	[31]
Yang L <i>et al.</i>	XELOX	42.9	7.1	82 days	Not available	[35]
Yin Z <i>et al.</i>	XELOX/FOLFOX6	55.0	5.0	2.1 months	9 months	[36]
He SL <i>et al.</i>	CAPEOX	62.5	21.9	4.2 months	9.2 months	[37]
Wang F <i>et al.</i>	FOLFOX4/XELOX	61.5	15.4	110 days	225 days	[40]
Liu S	S-1 plus oxaliplatin	47.6	19.0	Not available	Not available	[43]
Li S <i>et al.</i>	GEMOX	22.5	2.5	13.9 weeks	Not available	[48]
Yau T <i>et al.</i>	SECOX	78.0	16.0	5.29 months	11.73 months	[58]
Zhu AX <i>et al.</i>	GEMOX-B	47.0	20.0	5.3 months	9.6 months	[59]
Sun W <i>et al.</i>	XELOX plus bevacizumab	77.5	20.0	6.8 months	9.8 months	[60]
Adjuvant chemotherapy						
		Survival rates in the treatment group (%)		Survival rates in the control group (%)		
		1 year	3 years	1 year	3 years	
Chen J <i>et al.</i>	FOLFOX4/none	100	51.0	86.0	24.0	[69]
Li K <i>et al.</i>	FOLFOX4/best supportive care	77.8	33.3	54.5	17.5	[70]
Wang L <i>et al.</i>	Oxaliplatin, 5-U and calcium formyltetrahydrofolate/no post-transplant chemotherapy	89.7	86.2	64.5	53.6	[72]

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

was an international, multicenter, open-label, randomized, Phase III study that enrolled 371 patients with advanced HCC from 38 sites in the Asian-Pacific region. Several previous studies have shown that doxorubicin has limited anti-tumor efficacy and often been used in clinical practice. Also, doxorubicin was often used as the control group in the related research [13]. Using doxorubicin as the control arm in EACH study meet the ethical requirements and clinical realities of situation. Of the patients enrolled, 75% were from China (70% from mainland and 5% from Taiwan), 14% from Korea and 11% from Thailand. Patients were randomly assigned to receive either FOLFOX4 (n = 184) or doxorubicin (n = 187) until disease progression, intolerable toxicity, death, patient withdrawal of consent or until the patient became eligible for surgical resection, whichever occurred first. The FOLFOX4 regimen significantly improved the median progression-free survival (mPFS, 1.77 months in doxorubicin group vs 2.93 months in FOLFOX4 group; $p < 0.001$), response rate (RR, 2.67% in doxorubicin group vs 8.15% in

FOLFOX4 group; $p = 0.02$) and the disease control rate (DCR, 31.55% in doxorubicin group vs 52.17% in FOLFOX4 group; $p < 0.001$) when compared with doxorubicin alone [12]. The median overall survival (mOS) at the first analysis time-point was also longer in the FOLFOX4 group although it did not reach statistical significance (4.97 months in doxorubicin group vs 6.40 months in FOLFOX4 group; $p = 0.07$). After an additional 7 months of follow-up, the benefit on mOS become significant favoring the FOLFOX4 group (6.47 months in FOLFOX4 group vs 4.90 months in doxorubicin group; $p = 0.04$) [12]. For the Chinese patients included in the EACH study, the mOS was significantly longer in the FOLFOX4 group than in the doxorubicin alone group at the both cut-off dates [28]. The mOS at the first prespecified time point of treatment was 5.7 months with FOLFOX4 and 4.3 months with doxorubicin ($p = 0.03$). At the end of the follow-up period, the mOS was 5.9 months with FOLFOX4 and 4.3 months with doxorubicin ($p = 0.03$). Additionally, the mPFS, RR and DCR were significantly higher in the FOLFOX4

group than in the doxorubicin group (mPFS: 2.4 months vs 1.7 months; $p = 0.0002$; RR: 8.6 vs 1.4%; $p = 0.006$; DCR: 47.1 vs 26.6%; $p = 0.0004$). In terms of toxicity, the incidence of neutropenia and neurotoxicity was higher in the FOLFOX4 group, but the incidence of grade 3/4 toxicities was similar in both groups. Overall, the reported adverse events were consistent with those reported in previous clinical trials of FOLFOX4 in patients with colorectal cancer [29] with no other unexpected adverse events [28]. As compared with results reported with sorafenib in the ORIENTAL trial [3], which also enrolled HCC patients from the Asia-Pacific region, the results of the Chinese subgroup analysis of the EACH study [28] were of very similar magnitude in terms of OS and PFS, but with much better results in terms of RR and DCR.

The results of the EACH study were supported by the results of several smaller studies performed in Chinese patients [30,31]. In a single-center study, the FOLFOX4 regimen was administered as systemic chemotherapy in 77 Chinese patients with advanced HCC with or without previous chemotherapy for HCC [30]. The RR and DCR were 4.2 and 55.6%, respectively. Median time to progression (mTTP) was 2.7 months and mOS was 6.1 months. The stratified analysis showed a similar effect of this regimen both in untreated patients and in patients who previously received chemotherapy, but with a lower efficacy in patients with portal vein invasion or extrahepatic metastasis. The common adverse events were leukopenia and mild peripheral neurotoxicity [30]. Similar results were observed in another single center study, where 20 males with advanced HCC, recurrence or metastasis after multiple courses of TACE and no previous chemotherapy received systemic chemotherapy with the FOLFOX4 regimen [31]. Partial response (PR) was observed in four patients, stable disease (SD) in eight patients, and disease progression (PD) in eight patients. The mTTP was 2.2 months and the mOS 5 months [31].

In another study, the efficacy of the FOLFOX4 regimen associated with ultrasound-guided intratumor injection of a recombinant soluble tumor virus (H101, Shanghai Sunway Biotech) was assessed in 22 patients with advanced HCC [32]. Of the 20 patients treated with the FOLFOX4 regimen associated with ultrasound-guided intratumor injection of H101 and with evaluated objective efficacy, five got PR

and seven SD; the mTTP was 3.1 months [32]. Clinical symptoms, Karnofsky Performance Status score, and alpha fetoprotein (AFP) levels improved significantly in 11 of the 22 patients. The major adverse events were mild to moderate fever (45.6%), leukopenia (44.5%) and diarrhea (33.7%) [32]. H101 is a recombinant human type-5 adenovirus lacking the *E1B-55 kDa* gene responsible for *p53*-binding and inactivation [33]. Due to this deletion, it is not able to activate *p53* and replicate in normal cells, but it targets cancer cells which lack functional *p53* [34]. In humans, the antitumor activity of H101 was documented in refractory malignant tumors when administered in combination with chemotherapy [35].

• XELOX regimen (Tables 1 & 2)

After the combination of capecitabine with oxaliplatin (XELOX regimen) has been proved to be efficient in the treatment of colorectal cancer, its use in patients with advanced HCC was also investigated in several studies, most of them performed in China [36–38]. The justification for the use of this regimen in patients with advanced HCC was also based on the clinical efficacy (11% RR in monotherapy) and favorable toxicity profile of capecitabine in patients with liver cirrhosis [39], as well as due to the lack of need of adjustment of its dose in patients with mild and moderate hepatic dysfunction [39]. Recently, Yang L *et al.* [36] reported the results of a 31-patient open label study performed with the aim to evaluate the efficacy and safety of a modified XELOX regimen (oxaliplatin 150 mg was administered as intravenous infusion on Days 1 and 15; capecitabine 1000 mg with calcium folinate tablets 50 mg, twice a day on Days 1 to 14) administered every 4 weeks. This study showed encouraging results in terms of survival and disease control, with mild adverse events. The DCR was 42.9% and the mTTP was 82 days, with a survival rate of 68.2% at 6 months and 57.7% at 1 year. In another study, 40 patients with advanced HCC were randomly assigned to receive either XELOX therapy (20 patients) or FOLFOX 6 therapy (20 patients) for two cycles [37]. The study showed similar results in terms of efficacy with both treatment regimens: DCR was 55% in FOLFOX6 group and 50% in XELOX group; the mOS was 9 months and 10 months, respectively; and the 6-month survival rate was 33 and 38%, respectively ($p > 0.05$ for all comparisons) [37]. In terms of safety, the incidence of hand-foot syndrome was higher

and the incidence of gastrointestinal and hematological toxicities was lower in the XELOX group compared with the FOLFOX group ($p < 0.05$) [37]. In a further prospective study, 32 patients with extrahepatic metastasis of HCC after local treatment received oxaliplatin 100 mg/m² on day 1 and capecitabine 1000 mg/m² on days 1–14 [38]. The mTTP was 4.2 months (95%CI: 2.5–7.4), and the mOS time was 9.2 months (95%CI: 6.5–17.8) [38]. The mOS was longer in patients with a Child-Pugh class A (10.1 months) compared with class B patients (5.4 months). Grade 3–4 toxicities were reported for 11 patients (34.4%) [38].

Despite the established efficacy of sorafenib in advanced HCC, a high number of sorafenib-treated patients experience disease progression. Therefore, the administration of XELOX and FOLFOX regimens as second-line therapies in patients with disease progression following sorafenib first-line therapy may represent another treatment option. To test this hypothesis, Wang F *et al.* [41], assigned 16 patients from a single study center in China who had disease progression after sorafenib therapy, to receive either the FOLFOX4 regimen (nine patients) or the XELOX regimen (seven patients). Oral sorafenib was allowed as concomitant therapy if the duration of disease control for patients under sorafenib treatment was more than 3 months (five cases with XELOX regimen and three cases with FOLFOX regimen). PR was observed in two patients and SD in six patients, with an overall RR of 15.4% and DCR of 61.5%. The mTTP was 110 days and the mOS was 225 days. The major adverse events reported were bone marrow suppression (thrombocytopenia, leukocytopenia and neutropenia) which resolved after cytokine administration. It is worth mentioning that the patients who achieved partial response were those who continued to receive sorafenib during the FOLFOX4 therapy [41]. Thus, we can hypothesize that this positive response may be due to a synergistic antitumor effect of oxaliplatin-based regimens and sorafenib and that oxaliplatin-based regimens may reverse the resistance to sorafenib therapy [5].

• Oxaliplatin in combination with S-1 (Tables 1 & 2)

Another potential drug for the treatment of patients with advanced HCC maybe tegafur gimeracil oteracil (S-1), a oral fluorouracil-based drug consisting of a combination of tegafur,

gimeracil and oteracil potassium. Tegafur is a prodrug of 5-FU which has good oral bioavailability and converts to 5-FU *in vivo* [42]. Gimeracil has the capacity to inhibit the catabolism of 5-FU released from tegafur and maintains an effective concentration of 5-FU in the blood and the tumor tissue for longer periods of time [42]. Thus, its association with tegafur confers an efficacy similar to the continuous intravenous infusion of 5-FU in addition to the advantages of the oral administration. Oteracil inhibits the phosphorylation of 5-U after oral administration; high gastrointestinal concentrations of oteracil were observed after oral administration which may increase the distribution of 5-FU in the gastrointestinal tract and reduce adverse effects [42]. Therefore, at least at a theoretical level, for tumors (liver cancer, included) with high-activity of dihydropyrimidine dehydrogenase (DPD), S-1 may have higher efficacy than other FU-based drugs. Though the history results of treatment with 5-FU and its derivatives were controversial exploratory studies in this field were still being carried out. Based on positive results of phase I studies with S-1 in patients with HCC, therapy with both S-1 and oxaliplatin has been investigated in two small studies and showed promising results both in terms of safety and efficacy [43,44]. 21 patients with HCC who received S-1 with either cisplatin or oxaliplatin every 3 weeks either as a first-line or salvage treatment were retrospectively analyzed [43]. Of all enrolled patients, five achieved PR and six SD. The mTTP was 4.0 months and the mOS was 14.0 months. No grade 4 toxicity was reported in treated patients [43]. The analysis of DPD expression showed that efficiency of S-1 varies according to the level of DPD expression in the tumor; RR was 60.0% in patients with lower versus 0.0% in patients with higher DPD expression ($p = 0.045$) [43]. Liu S [43] combined S-1 and oxaliplatin for the treatment of 42 patients with advanced HCC. Tumor response was observed in eight patients and SD in 12 patients, while clinical symptoms were significantly improved or disappeared in 22 (52%) patients. Major adverse reactions were mild neurotoxicity (in 17% of the patients) and of a hematological nature [44].

• GEMOX regimen (Tables 1 & 2)

The results of a Phase II and pilot studies highlighted the GEMOX regimen as an attractive therapeutic option in patients with advanced

HCC due to its efficacy and the absence of renal and hepatic toxicity in cirrhotic patients [45–47]. The Association des Gastro-Entérologues Oncologues (AGEO) study [48] which retrospectively analyzed the activity of this regimen in real life conditions, enrolled 204 consecutive patients with HCC treated with GEMOX and showed that this regimen was effective and had an acceptable safety profile. The response induced by GEMOX allowed a secondary local therapy option in selected patients and proved to be an alternative after sorafenib discontinuation. The use of GEMOX in HCC patients have been also reported in Chinese patients, with similar results [5,49]. In a study enrolling 40 patients with unresectable, non-embolizable HCC and no prior systemic chemotherapy, it was shown that GEMOX therapy was associated with mild toxicities [49]. In terms of efficacy, one patient had PR, eight SD and the mTTP was 13.9 weeks [49]. It should be noted that in several of the studies performed in China, the GEMOX regimen was slightly modified including a higher dose of gemcitabine. Gemcitabine 1000 mg/m² was administered as an intravenous infusion at Days 1 and 8 and oxaliplatin 100–130 mg/m² as an intravenous infusion at Day 2, in 3-week cycles [5].

Efficacy & safety of chemotherapy with oxaliplatin in combination with molecular target therapy

• Sorafenib (Tables 1 & 2)

Currently, sorafenib is the only available molecular targeted therapy drug with proven survival benefits in the of advanced HCC patients and approved worldwide for the treatment of these patients. However, due to high rates of infection with hepatitis viruses [50], its efficiency as a single-agent therapy in patients from the Asia-Pacific region is limited, with a very low RR of 2–3% and a median survival period of up to 2.3 months [3]. In patients from European and American, where the main cause is hepatitis C, RR was 2% and median survival time extended 2.8 months [4]. Additionally, its effect on tumor size is limited due to the mechanism of action [3,4]. Although a head-to-head comparison of sorafenib therapy and systemic chemotherapy in Chinese or Asian patients does not exist, a retrospective study analyzing the data from 220 Korean patients with HCC and HBV infection have shown a trend of higher efficacy of systemic chemotherapy compared with sorafenib in the

majority of cases [51]. The mOS was 7.2 months and 11.2 months in the sorafenib and cytotoxic chemotherapy groups, respectively ($p = 0.10$), and the mPFS was 3.2 months and 5.9 months, respectively ($p = 0.07$) [51].

Sorafenib exerts its antitumor activities by targeting tumoral angiogenesis through inhibition of VEGF action [52–54] and aberrant mitogen-activated protein kinases (MAPK) signaling [53–55]. Oxaliplatin inhibits cell cycle progression and induces apoptosis through activation of *p53* pathway [17,18]. Due to their different mechanisms of action, it was first hypothesized and recently proven in BEL-7402 cell lines that the combination of oxaliplatin with sorafenib has a synergistic antiproliferative activity [56]. Therefore, a valid reason for studying combinations of sorafenib with oxaliplatin-based regimens agents in an attempt to improve survival has been established.

The combination of sorafenib with GEMOX was assessed in European patients in a randomized Phase II trial (GONEXT) [57]. The trial randomized 95 patients with advanced HCC, good performance status and liver function to either sorafenib alone or GEMOX plus sorafenib [57]. The efficacy data were encouraging: the 4-month PFS rate was 61% in the combination group compared with 54% in the sorafenib monotherapy group; the PFS was 6.2 months versus 4.6 months; the RR was 16 versus 9%; and the DCR was 77 versus 70%, respectively [57]. No data on the efficacy of this combination have been reported in Chinese patients yet, although the combination of sorafenib with oxaliplatin and capecitabine (a prodrug that is enzymatically converted to 5-FU [57]) – SECOX – has also been tested with encouraging results [59]. A single-arm, multicenter Phase II study was performed in 51 Asian patients with advanced HCC to assess the efficacy and tolerability of the SECOX regimen [59]. 84% of the patients had chronic hepatitis B infection, 90% had BCLC stage C disease and 80% of the patients had extrahepatic metastasis [59]. The median TTP was 5.29 months (95% CI: 3.81–5.88 months), mPFS 5.26 months (95% CI: 3.75–5.88 months) and mOS 11.73 months (95% I: 8.87–15.38 months). The most frequently reported adverse events were diarrhea (75%) and hand–foot–skin reaction (73%) with the majority of patients having grade one or two, a little higher than the result of sorafenib monotherapy [59].

• Monoclonal antibodies (Tables 1 & 2)

A number of monoclonal antibodies that bind the VEGF and inhibit angiogenesis are currently under evaluation in several clinical trials [60–64]. In general, the trials reported good efficacy but the relatively high number of adverse events such as arterial/venous thrombotic events and variceal hemorrhage is of concern [60–65]. Of the monoclonal antibodies under evaluation, bevacizumab, a monoclonal antibody against VEGF, has shown antitumor activity, an encouraging OS and 6 months PFS in combination with GEMOX in Chinese patients [60]. In a Phase II study assessing the association of the XELOX regimen with bevacizumab, the mPFS was 6.8 months (95% CI: 3.4–9.1 months), the mOS was 9.8 months (95% CI: 5.2–12.1 months) and the overall DCR 77.5%. The combination was well tolerated with limited grade 3/4 toxicity [61]. Good results were also reported by Ku GY *et al.* [66] in a series of five cases (four with cirrhosis) treated with a combination of bevacizumab, oxaliplatin and doxorubicin (or liposomal doxorubicin); the AFP levels of four patients decreased by more than 50% compared with the baseline levels; one patient achieved radiographic complete response and one stable disease.

Cetuximab is an IgG1 monoclonal antibody which can competitively inhibit the binding of ligands to EGFRs, and block the intracellular signal transduction pathway [67]. Thus, cetuximab interferes with the growth, invasion and metastasis of tumor cells, inhibits cell repair and angiogenesis, and induces apoptosis [67]. Although it has limited efficacy as monotherapy in advanced HCC, it has a good safety profile [62]. Based on the successful experience of the association of cetuximab with systemic chemotherapy in the treatment of colorectal cancer [67], the association of this monoclonal antibody with the GEMOX and XELOX regimens was studied but no results are available for Chinese patients. The Phase II studies performed in European patients have shown promising efficacy results and acceptable toxicity [63,64].

Adjuvant Oxaliplatin chemotherapy (Tables 1 & 2)

Recurrence and metastasis have been shown to occur in more than 50% of the HCC patients treated with radical resection or liver transplant operation [68]. Currently, there is no standard adjuvant therapy following HCC resection. The highly expected results of the placebo-controlled

STORM trial showed that sorafenib had no effect on HCC recurrence and 30% of patients in the sorafenib arm had discontinued treatment at 3 months after treatment initiation, and almost 50% by 1 year [69]. In the last years, oxaliplatin-based regimens have been used as adjuvant chemotherapy in Chinese patients with good results [70–72]. A retrospective analysis of 115 patients with HCC which received either FOLFOX4 after radical resection or no adjuvant chemotherapy, showed that FOLFOX4 regimen could delay tumor recurrence and improve the overall survival rate [70]. The median time to tumor recurrence (mTTR) in control group and FOLFOX4 group were 11.9 months and 14.9 months, respectively ($p = 0.026$); overall survival rates at 1, 2, 3 and 5 years were 86, 60, 24 and 9%, respectively, in the control group and 100, 78, 51 and 17%, respectively, in the FOLFOX4 group ($p = 0.004$) [69]. These positive results were further confirmed in a randomized trial which showed significantly higher survival rates in FOLFOX4 at 1, 2 and 3 years (77.8, 64.4 and 33.3%, respectively) when compared with supportive care (54.5, 40.9 and 17.5%, respectively; $p = 0.02$) [71]. No difference was observed between groups in terms of recurrence [71].

Xiao *et al.* [72] analyzed 120 HCC patients who received TACE as adjuvant therapy (88 patients; 43 patients received combined gemcitabine and oxaliplatin TACE drugs), systemic chemotherapy (45 patients) or no adjuvant chemotherapy (32 patients). In the TACE group, the intrahepatic recurrence rates at 6 and 12 months (20.5 and 43.8%) were significantly lower than in the group receiving systemic chemotherapy (37.5 and 59.4%; $p < 0.05$), as was the 6-months recurrence rate (11.6 vs 28.9%; $p < 0.05$) [71]. No difference between groups was observed in terms of the 12-month recurrence rate. The incidence of treatment-related adverse events (leukopenia, nausea and emesis) was lower in the TACE group compared with the systemic chemotherapy group ($p < 0.05$) [72].

The efficacy and safety of oxaliplatin-based regimens have been also studied in patients with orthotopic liver transplantation for advanced HCC and cirrhosis. Wang L *et al.* [73] randomized 58 patients to either no post-transplant chemotherapy or up to six-cycle adjuvant therapy with oxaliplatin, 5-FU and calcium formyltetrahydrofolate. The study showed good efficacy of the adjuvant chemotherapy in these patients. The 1-, 2- and 3-year survival rates were significantly

higher in the group receiving adjuvant chemotherapy compared with the control group (89.7, 86.2 and 78.8% vs 64.5, 61.1 and 53.6%, respectively; $p = 0.001$) [73]. The tumor-free survival rate was also significantly higher at 1 year post-transplant (73.9 vs 58.1%; $p = 0.001$), but the difference was not significant at 3 years (44.2 vs 38.6%; $p > 0.05$) [73]. The major adverse event related to chemotherapy administration was bone marrow suppression (leukopenia in 24 patients and thrombocytopenia in seven patients). Of note, no patient discontinued the treatment due to adverse events related to chemotherapy administration [73].

Though most of these studies were single-center, small sample size and the level of evidence was low, results demonstrated some effect and a favorable trend, we await confirmation by large sample, randomized controlled Phase III clinical studies.

Conclusions

In conclusion, the current evidence suggest that oxaliplatin-based regimens are relatively efficient and have an acceptable level of toxicity when used for the treatment of advanced HCC in Chinese patients. The results of the EACH study, which showed that systemic chemotherapy with an oxaliplatin-based regimen could improve survival have redefined the treatment of Asian patients with advanced HCC and especially the treatment of Chinese patients with advanced HCC patients [12,28]. Thus besides the Clinical Guideline for Diagnosis and Treatment of Primary Liver Cancer published by the National Health and Family Planning Commission of the People's Republic of China, treatment plan for HCC proposed by the KLCSSG and NCC in Korea and new NCCN Guideline in American also include systemic chemotherapy as one important option

for advanced HCC [74,75]. Additionally, the association of oxaliplatin with other cytotoxic drugs (such as capecitabine and gemcitabine) or molecular targeted therapy (sorafenib, bevacizumab) has been shown to improve survival in Chinese patients, but the results came from small size studies. Large-scale, randomized and controlled clinical studies are needed to further investigate these treatment options.

Future perspective

In the future, it is urgent to continue to carry out clinical research, especially the transformation research, to make clear the best model of the combination of oxaliplatin and other therapeutic agents and means. At the same time, we should deeply explore the mechanism of oxaliplatin resistance with the advanced technology of molecular biology, summarize the characteristics of the effective population and find the clinical characteristics and/or molecular markers for predicting the efficacy. Moreover, as the main causes of HCC, clinical manifestations, clinical stages, speed of disease development and co-morbidities vary from one person to another, the combination of various therapeutic strategies should be individualized. Further research in the fundamental science on the synergy of the anti-tumor molecules may provide additional support for therapeutic decisions.

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