

Cytotoxic Chemotherapy as an Alternative for Systemic Treatment of Advanced Hepatocellular Carcinoma in Developing Countries

This article was published in the following Dove Press journal:
Cancer Management and Research

Khaled Abouelezz¹
Dipen Khanapara¹
Gaber El-Saber Batiha²
Esraa A Ahmed^{3,4}
Helal F Hetta^{1,5}

¹Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA; ²Department of Pharmacology and Therapeutics, Faculty of Veterinary Medicines, Damanhour University, Damanhour 22511, Egypt; ³Department of Pharmacology, Faculty of Medicine, Assiut University, Assiut 71515, Egypt; ⁴Centre of Excellence in Environmental Studies (CEES), King Abdulaziz University, Jeddah 21589, Saudi Arabia; ⁵Department of Medical Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut 71526, Egypt

Abstract: Systemic therapy options nowadays for advanced hepatocellular carcinoma (HCC) are either immunotherapy with immune checkpoint inhibitors or targeted therapy. As the incidence of liver cancer is much higher in developing countries, these new medications are not readily accessible for most of the patients. Cytotoxic chemotherapy agents are more available and affordable in developing countries. We are trying to explore the effectiveness of the newer cytotoxic agents in the systematic treatment for advanced HCC. This is a systematic review of all randomized controlled trials since 1997 that utilized systemic cytotoxic chemotherapy agents in the systemic treatment for advanced HCC using Scopus, PubMed, and Cochrane library up to February 2020. Six randomized trials were found. Different drugs and dosages were used, so it was statistically inappropriate to conduct a meta-analysis. No Phase III trial showed statistically significant overall survival (OS) benefit for cytotoxic chemotherapy, except subgroup analysis of Chinese patients in one study who had leucovorin, fluorouracil, and oxaliplatin (FOLFOX) regimen. There was no significant progression-free survival (PFS) or response rate in the Phase II trials. There are not enough data to infer the actual benefits of systemic cytotoxic chemotherapy in advanced HCC. However, oxaliplatin-based regimens may give feasible results. Health systems with limited access to targeted therapy and immunotherapy agents may use oxaliplatin-based regimens in clinical trials for advanced HCC. These results should be confirmed in multiple future randomized clinical trials.

Keywords: HCC, randomized trials, sorafenib, oxaliplatin

Introduction

Liver cancer is the sixth most common cancer and the fourth most common cause of death from cancer in the world.^{1,2} The median survival of advanced hepatocellular carcinoma (HCC) is seven and six months for Barcelona Clinic Liver Cancer (BCLC) stage C and D, respectively, for untreated patients.³ For about ten years, sorafenib was the only standard systemic treatment for patients with HCC who are not candidates for resection or local treatment. That was based mainly on SHARP and Asia-Pacific trials.^{4,5} Recently, there are multiple targeted therapies, and immunotherapy agents were approved for the systemic treatment for HCC. Lenvatinib was approved by the food and drug administration (FDA) in August 2018 as a first-line treatment for patients with unresectable HCC based on REFLECT trial.⁶ Regorafenib, nivolumab, pembrolizumab, and cabozantinib were approved as second-line therapy for HCC, while ramucirumab was

Correspondence: Helal F Hetta
Department of Medical Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut 71526, Egypt
Email helalhetta@aun.edu.eg

approved as second-line therapy for patients with alpha-fetoprotein ≥ 400 .⁷ A recent study using atezolizumab with bevacizumab showed an overall survival and progression-free survival benefits over sorafenib for the first time.⁸

The cost and availability of targeted therapy in developing countries are significant problems. Eighty-three percent of estimated new liver cancer cases were found in less developed countries in 2012.⁹ When targeted therapy is not available, the other option will be supportive care only for most of the patients, as historically cytotoxic chemotherapy did not have remarkable results in the treatment of advanced HCC.¹⁰ In a systematic review of randomized controlled trials for chemotherapy in advanced HCC till 1997, almost all the trails used doxorubicin or doxorubicin analogs. The results were mixed, but no remarkable benefits were found, and toxicity was significant.¹¹ Since that time, many cytotoxic agents were developed, but no precise data about their effect on systemic treatment for HCC. In this review, we will explore all randomized trials since 1997 that used cytotoxic chemotherapy drugs, single or combined, in the systemic treatment of advanced HCC in adults in comparison to other systemic treatments. We will review study design, patients' characteristics, overall survival benefits, tumor response, progression-free survival, and toxicity from cytotoxic agents.

Methods

A search was conducted in the electronic database using Scopus, PubMed, and Cochrane library. A review of the reference lists of retrieved articles was done as well. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.¹² The search was done through February 29th, 2020.

For Scopus, the keywords used are Hepatocellular carcinoma, randomized, systemic chemotherapy, gemcitabine, oxaliplatin, doxorubicin, capecitabine, and cisplatin. Not locoregional or chemoembolization.

Inclusion Criteria

- All randomized controlled trials that are in English and published as a full article since 1997.
- Systemic cytotoxic chemotherapy is used exclusively as one of the arms of the study for the treatment for advanced HCC (single of multiple cytotoxic chemotherapy agents as one of the arms of the study).
- Participants are adult patients with advanced hepatocellular carcinoma with any etiology.

- The study should have an independent concurrent control arm.

Exclusion Criteria

- Chemotherapy was used as adjuvant or neoadjuvant therapy.
- Chemotherapy is used as a local injection (Transarterial chemoembolization TACE).
- Studies that were published as abstract only.
- Non-cytotoxic chemotherapy agents are used with cytotoxic chemotherapy arm.

Quality Assessment

The authors included only the articles that fulfilled the above criteria. Both authors reviewed and assessed the data independently.

Analysis of Data

- Studies design and characteristics (Table 1),
- Patients' characteristics (Table 2),
- Outcome: Median overall survival, progression-free survival, objective response, and side effects (Table 3).
- As different drugs and dosing regimens were used, it was not appropriate to conduct a Meta-Analyses.

Results

Four hundred thirty-seven articles were found with the initial search, 151 were excluded as they were duplicate. Two hundred eighty-six articles were examined; 269 articles were excluded as they were either non-randomized trials, systematic reviews, or expert opinion. Seventeen articles were examined in detail, 11 were excluded as they did not use cytotoxic chemotherapy exclusively at least in one of the study arms or used chemotherapy as adjuvant or neoadjuvant treatment.

Study Characteristics

Six studies have met the criteria (Figure 1). Three of these studies were Phase II, and the others were Phase III. All, except one,¹³ were designed before the approval of sorafenib. A single study was double-blinded,¹⁴ while the others were open-label trials. All of them used doxorubicin as a control arm, except one used sorafenib.¹³ Three of these studies used the combination regimen.¹⁵⁻¹⁷ To evaluate the response, three of them used WHO criteria,^{14,16,18} the other three used Response Evaluation Criteria in Solid

Table 1 Studies Design and Characteristics

Study	Abdel-Rahman et al ¹³	Qin et al ¹⁵	Gish et al ¹⁴	Yeo et al ¹⁶	Abou Alfa et al ¹⁷	Mok et al ¹⁸
Type of Study	Phase II Randomized Open Label	Phase III Randomized Open Label	Phase III Randomized Open Label	Phase III Randomized Open Label	Phase II Randomized Double-Blind	Phase II Randomized Open Label
Study arms	Sorafenib Capecitabine	FOLFOX4 Doxorubicin	Nolatrexed Doxorubicin	Doxorubicin	Doxorubicin + sorafenib Doxorubicin + placebo	Doxorubicin Nolatrexed
Dosage/frequency	400mg BID daily 1000mg/m ² bid d 1-14	Oxa: 85mg/m ² d1 LV200mg/m ² d1 and 2, FU 400mg/m ² then 600mg/m ² over 22hr every 2 wks	800mg/m ² CI over 5 days/3ws 60mg/m ² every 3ws	60mg/m ² every 3 weeks P: 20 mg/m ² d1-4 I: 5 MU/m ² d 1-4 A: 40mg/m ² D1, F: 400 mg/m ² D1-4 every Wk	60 mg/m ² every 21 days 60 mg/m ² every 21 days +	725 mg/m ² over 5 days every 3 weeks 60mg/m ² d1 every 3 weeks
Number in each arm	26 26	184 187	222 223	94 94	47 49	18 36
Main inclusion criteria	<ul style="list-style-type: none"> No previous therapy Not a candidate for surgery or local treatment 	<ul style="list-style-type: none"> KPS ≥70 Not a candidate for surgery or local treatment Has HBV or HCV with cirrhosis If previous adjuvant CTX should be completed more than 12 ms 	<ul style="list-style-type: none"> KPS ≥ 60% CLIP scores ≤3 Adequate liver function LVEF ≥50% 	<ul style="list-style-type: none"> Unresectable or metastatic cancer Total bilirubin ≤ 1.75 mg/dl Uncontrolled ascites 	<ul style="list-style-type: none"> No prior chemotherapy LVEF ≥45% 	<ul style="list-style-type: none"> KPS ≥ 70 Bilirubin No prior CTX within 4 weeks only
Main exclusion criteria	<ul style="list-style-type: none"> Renal failure on dialysis CHF NYHA > class II Active CAD Metastatic brain cancer Concurrent Cancer 	<ul style="list-style-type: none"> Previous oxaliplatin or doxorubicin treatment except adjuvant more than 12ms Previous liver transplant CNS metastasis Serious illness 	<ul style="list-style-type: none"> Resectable liver lesion Transplant candidate (included later) Prior doxorubicin or liposomal doxorubicin Severe intercurrent illness 	<ul style="list-style-type: none"> Any history of cancer except NM skin cancer Bone & brain mets Prior CTX Serious illness 	<ul style="list-style-type: none"> Prior TA chemoembolization Psychological or social problem Fibrolamellar or mixed histology 	<ul style="list-style-type: none"> Bilirubin >3 mg/dL, AST or ALT >5.0 × upper normal limit or albumin <3 g/d Uncontrolled ascites Another malignancy within 5 years of randomization

(Continued)

Table 1 (Continued).

Study	Abdel-Rahman et al ¹³	Qin et al ¹⁵	Gish et al ¹⁴	Yeo et al ¹⁶	About Alfa et al ¹⁷	Mok et al ¹⁸
Type of Study	Phase II Randomized Open Label	Phase III Randomized Open Label	Phase III Randomized Open Label	Phase III Randomized Open Label	Phase II Randomized Double-Blind	Phase II Randomized Open Label
Methods of assessment	Baseline Follow-up	CT or MRI 6w± I during treatment 2ms ± lw in follow-up	NS NS	CT ± US After 3 and 6 cycles of treatment	NS NS	CT or US Repeat imaging with every cycle
Response criteria	RECIST 1.0 for response	RECIST 1.0	WHO criteria for partial and complete response	WHO criteria	RECIST 1.0	WHO criteria for partial and complete response

Abbreviations: CLIP; cancer of the liver Italian program; CI, continuous infusion; FU, 5 fluorouracil; LV, leucovorin; mets, metastases; NS, non-specified; PIAF, cisplatin/interferon α -2b/doxorubicin/fluorouracil; KPS, Karnofsky performance status; RECIST, response evaluation criteria in solid tumors; Oxa, oxaliplatin; TA, transarterial.

Tumors (RECIST) 1.0.^{13,15,17} In the studies that gave patients’ characteristics, most of their patients were male. Baseline performance either between 0–2 according to ECOG performance status or above 60% according to Karnofsky Performance status (KPS) scale. All were Child-Paugh A or B. The studies used different staging systems but mainly Barcelona Clinic Liver Cancer staging system. For possible underlying etiology, patients with HBV infection were the majority in three of the studies.^{15,16,18} The majority of patients had HCV infection in one study.¹³

Outcomes

It was challenging to do a statistically meaningful meta-analysis as these studies used different cytotoxic agents, and different doses (doxorubicin was used in most of these studies in different doses as the control arm, and it is known that doxorubicin has poor results in HCC). Median overall survival (OS) was the primary outcome of phase III studies.^{14–16} OS in these studies, for control arm (doxorubicin), was ranging between 4.79 and 7.43 months. Longest median overall survival was 8.67 months in Yeo et al study at cisplatin/interferon α -2b/doxorubicin/5-fluorouracil (PIAF) arm, but that was not statistically significant with p-value 0.86.¹⁶ In a large phase III trial, nolatrexed showed lower median overall survival than doxorubicin, as OS was 5.13 and 7.43 months, respectively, with p-value 0.0068.¹³ FOLFOX showed better OS than doxorubicin with OS 6.4 months and 4.79 months, respectively, but that study did not meet its primary endpoint with p = 0.07.¹⁵ The highest tumor response was at PIAF arm at Yeo et al study, as the response rate was 20.9%, but all responses were partial with no complete response.¹⁶ FOLFOX arm at Qin et al study showed a good partial response but no complete response; the response rate was 8.15%.¹⁵ In phase II trials, response rate and progression-free survival were not significant for capecitabine and nolatrexed.^{13,18} Side effects of doxorubicin in all studies were mainly neutropenia, anemia, alopecia, and fatigue. FOLFOX’s main non-hematological side effects were nausea, AST elevation, and anorexia. For hematological side effects, 30.6% had grade 3 to 4 neutropenia.¹⁵ PIAF regimen toxicities were significant and were mainly neutropenia, thrombocytopenia, and hypokalemia.¹⁶ Nolatrexed showed stomatitis, vomiting, diarrhea, and thrombocytopenia.¹⁴ Two studies were not completed; Mok et al study was discontinued as there was no objective response in nolatrexed arm.¹⁸ The

Table 2 Patients' Characteristics (Age, Sex, Status, Child-Pugh Score, Stage, Etiology)

Study	Abdel-Rahman et al. ¹³	Qin et al. ¹⁵	Gish et al. ¹⁴		Yeo et al. ¹⁶		Abou Alfa et al. ¹⁷		Mok et al. ¹⁸
			Nolatrexed	Doxorubicin	Doxorubicin	PIAF	Doxorubicin+ Sorafenib	Doxorubicin	
Age	53.5 (median)	18-75	NS		15-75		38-82 (median 65y)		> 18y
Sex	Mainly males	88.7%males	NS		91% males		76% males		90.7% males
Baseline status	ECOG PST 0-2	KPS ≥70	KPS ≥ 60		ECOG PST 0-2		ECOG PST 0-2		KPS ≥ 70
Child-Pugh	A-B	A(87.9%)-B(12.1%)	A 74.8% B 24.3%	A 73.1% B 26.9%	A 87.2% B 12.8%	A 83% B 17%	A		NS
Stage	BCLC C	BCLC B(20%) or C (80%)	Using CLIP score 35.1% score 2 29.3% score 3 27.9% score 1	35.9% score 2 28.7% score 2 27.4% score 2	Okuda staging I 9% II 87% III 4% II 4%	I 9% II 87% III 4%	NS		NS
Possible etiology	HCV 96% HBV 2% NASH 2%	HBV 91.4% HCV 6.7%	HCV 35.6% HBV26.1% History of Alcoholism 29.3%	HCV 43% HBV18.4% History of Alcoholism 26%	HBV 85% HCV 9%	HBV 87% HCV 4%	HBV 6.4% HCV 21.3%	HBV 14.3% HCV 14.3%	HBV 78%

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; KPS, Karnofsky performance status; NASH, non-alcoholic steatohepatitis; PIAF, cisplatin/interferon α -2b/doxorubicin/fluorouracil; PST, performance status.

Table 3 Outcome Median Overall Survival, Progression-Free Survival, Objective Response and Side Effects

Study	Abdel-Rahman et al ¹³		Qin et al ¹⁵		Gish et al ¹⁴		Yeo et al ¹⁶		Abou Alfa et al ¹⁷		Mok et al ¹⁸	
	Study arm	Capecitabine	FOLFOX	Doxorubicin	Nolatrexed	Doxorubicin	Doxorubicin	PIAF	D+S	D+P	Nolatrexed	Doxorubicin
Progression-free survival	6m	4m	2.93m	1.77m	2.76m	2.3m	NS	NS	6m	2.7m	1.58m	1.5m
	p < 0.005, HR 2.708											
Median overall survival	7.05m	5.07m	6.4m	4.79m	5.13m	7.43m	6.83m	8.67m	13.7m	6.5m	4.6m	3.4m
	p < 0.016, HR 2.36											
Main adverse event	Hand and foot syndrome, gastrointestinal	Hyperbilirubinemia, gastrointestinal	Neutropenia, Nausea, ↑ AST, anorexia	Alopecia, ↑ AST, Nausea	Stomatitis, Vomiting, Diarrhea, Thrombocytopenia	Alopecia, Neutropenia, Anemia	Neutropenia, Anemia, Thrombocytopenia	Neutropenia, Thrombocytopenia, Hypokalemia	Leucopenia, Hand & foot skin reaction, Diarrhea, Systolic dysfunction	Fatigue, Neutropenia, Diarrhea	Neutropenia, Stomatitis, Anemia, vomiting	Neutropenia, Anemia, Alopecia
Partial response	3pts	1pt	15	5	NS	NS	9	19	2	0	0	0
Complete response	1pt	0	0	0	NS	NS	0	0	0	1	0	0
Response rate	14.5%	3%	8.15%	2.67%	1.4%	4%	10.5%	20.9%	4%	2%	0	0
	p= 0.00668, HR 0.753											
	p= 0.83, HR 0.97											
	p= 0.006, HR: 0.45											
	p = 0.9843											

Abbreviations: m, month; HR, hazard ratio; D+S, doxorubicin+sorafenib; D+P, doxorubicin+placebo; NS, not specified.

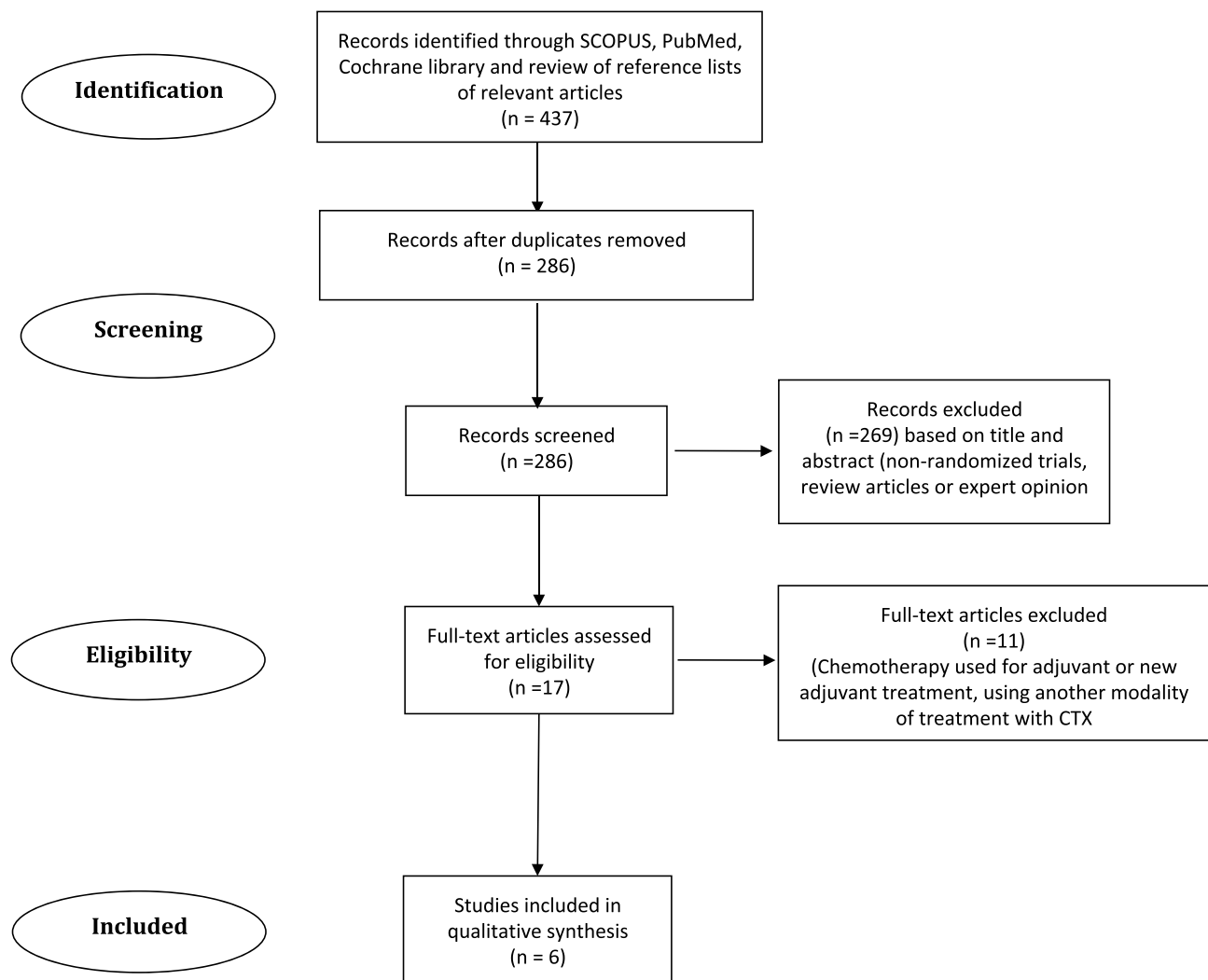


Figure 1 Flow chart of study selection.

other study was not completed after interim analysis, as it showed significant differences between sorafenib + doxorubicin arm and doxorubicin + placebo arm.¹⁷

Discussion

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide. More than 80% of HCC cases occur in low-resource and middle-resource countries where medical and social care resources are often constrained. One of the common risk factors for HCC is chronic hepatitis B and chronic hepatitis C (CHC) infection.^{19–26}

Advanced hepatocellular carcinoma is a challenging disease with different epidemiology and risk factors based on demographics worldwide.^{27,28} There was no universal approved drug for systemic treatment of advanced HCC until the approval of sorafenib. As sorafenib showed

short overall survival benefit and modest response, clinical trials have been ongoing in that field. Kinase inhibitors other than sorafenib, like Lenvatinib, cabozantinib, and regorafenib, showed some good results, but none were superior to sorafenib.²⁹ As HCC is known to be a highly vascular tumor, drugs that act as vascular endothelium growth factor inhibitors with different mechanisms have been investigated as bevacizumab and Ramucirumab. Multiple drug categories have been investigated like a-Fetoprotein Targeted Drugs, and Glypican-3 Targeted Drugs.²⁹

The liver is a central immunomodulator that keeps the balance between protection and immunotolerance.^{30,31} Deregulation of the liver immunological network is a hallmark of chronic liver disease and HCC.^{32–39} Immunotherapy has been recently used for multiple types of cancer and has raised hope for the successful treatment

of advanced HCC. Immune Checkpoint inhibitors have been used for treatment as a single agent or in combination with targeted therapy or VEGF inhibitors with promising results, as atezolizumab, Pembrolizumab, and Nivolumab.^{40,41} Many clinical trials are ongoing to investigate the effect of Chimeric antigen receptor T (CAR-T) cell therapy on HCC.⁴⁰

In developing countries, the cost of these new medications can be a challenge due to limited resources. Many studies showed that sorafenib is not a cost-effective option for advanced HCC in some developing countries.^{42–44} Cytotoxic chemotherapy drugs are more available and cheaper, but historically, systemic cytotoxic chemotherapy did not show noteworthy results, but local cytotoxic chemotherapy agents have been used frequently. Transarterial Chemoembolization (TACE) with cytotoxic chemotherapy drugs have been used as a single modality of treatment or in combination with other locoregional modalities, like three-dimensional conformal radiotherapy, percutaneous ethanol injection, percutaneous microwave coagulation therapy, and percutaneous acetic acid injection.^{45,46} The most common chemotherapy combinations that have been used for TACE are Fluorouracil, cisplatin, mitomycin, and epirubicin.⁴⁷ Using systemic therapy (specifically sorafenib) with TACE is controversial. The side effects of the combination of sorafenib and the cytotoxic agents for TACE were significant, but the combination of hydroxycarbonythecin plus pirarubicin or epirubicin did not increase the side effects with improving efficacy.⁴⁸

The use of systemic cytotoxic chemotherapy alone in the treatment of HCC is rare since the approval of sorafenib. Doxorubicin was the most common drug to be used in these studies as a control arm, but there is no benefit of analyzing doxorubicin results together as it is evident from previous literature that it has little benefits with high toxicity. There are only three phase III trials that have used single cytotoxic chemotherapy drugs or in combination with other cytotoxic chemotherapy drugs as an arm of a trial in systemic treatment for advanced HCC over the last twenty years. PIAF study had a better OS over doxorubicin, but that was not statistically significant, and the toxicity was high.¹⁶ Nilotrexed did not show a survival benefit over doxorubicin.¹³ Although the third phase III study, which has used FOLFOX against doxorubicin, did not show statistically significant overall survival,¹⁵ in a subgroup analysis for Chinese patients in that study, there was a statistically significant overall survival. Median overall survival was 5.7 months and

4.3 months for FOLFOX4 and doxorubicin, respectively, HR 0.74; 95% CI: 0.55–0.98; p-value 0.03.⁴⁹ Based on that, China Food and drug administration approved oxaliplatin for the treatment of advanced HCC patients who are not eligible for a transplant or local treatment.⁵⁰ However, we should consider that most of the patients in that study had HBV infection, and that is not the most common etiology in different areas of the world. Phase II trials were included to examine response rate and progression-free survival. Capecitabine, nilotrexed, and doxorubicin did not show significant PFS or response rate in these studies. Other than these randomized trials, studies showed a survival benefit for some of the cytotoxic drugs as gemcitabine and oxaliplatin. In a retrospective study for two hundred and four patients who had Gemcitabine/Oxaliplatin combination (GEMOX) for HCC treatment, the median overall survival was 11 months (95% CI: 9–14), and the response rate was 22%.⁵¹ Other small trials using gemcitabine and oxaliplatin showed good tumor response.^{52,53} For toxicity, oxaliplatin-based regimens for the treatment of advanced HCC are relatively safe and well tolerated.⁵⁴

Limitations

There are few randomized trials utilized systemic cytotoxic chemotherapy exclusively. Three of the trials that were retrieved had a small sample size that affected the statistical results of these studies. Also, no study mentioned the subtypes of HCC in their patients, and that can make a difference in the outcome.

Conclusions

There is not enough data to infer the actual benefits of systemic cytotoxic chemotherapy in advanced HCC. But, oxaliplatin-based regimens may give feasible results. Health systems with limited access to targeted therapy and immunotherapy agents may use oxaliplatin-based regimens in clinical trials for advanced HCC. These results should be confirmed in multiple future randomized clinical trials.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest.

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
- Hetta HF, Mekky MA, Zahran AM, et al. Regulatory B cells and their cytokine profile in HCV-related hepatocellular carcinoma: association with regulatory T cells and disease progression. *Vaccines*. 2020;8(3):380. doi:10.3390/vaccines8030380
- Giannini EG, Farinati F, Ciccarese F, et al. Prognosis of untreated hepatocellular carcinoma. *Hepatology (Baltimore, Md)*. 2015;61(1):184–190. doi:10.1002/hep.27443
- Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–390. doi:10.1056/NEJMoa0708857
- 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. doi:10.1016/S1470-2045(08)70285-7
- Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised Phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1
- Vogel A, Saborowski A. Current strategies for the treatment of intermediate and advanced hepatocellular carcinoma. *Cancer Treat Rev*. 2020;82:101946. doi:10.1016/j.ctrv.2019.101946
- Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
- Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359–386. doi:10.1002/ijc.29210
- 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. doi:10.1093/jjco/27.5.321
- Simonetti RG, Liberati A, Angiolini C, Pagliaro L. Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. *Ann Oncol*. 1997;8(2):117–136. doi:10.1023/A:1008285123736
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
- Abdel-Rahman O, Abdel-Wahab M, Shaker M, Abdel-Wahab S, Elbassiony M, Ellithy M. Sorafenib versus capecitabine in the management of advanced hepatocellular carcinoma. *Med Oncol*. 2013;30(3):655. doi:10.1007/s12032-013-0655-z
- Gish RG, Porta C, Lazar L, et al. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nilotrexed or doxorubicin. *J Clin Oncol*. 2007;25(21):3069–3075. doi:10.1200/JCO.2006.08.4046
- 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. doi:10.1200/JCO.2012.44.5643
- 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. doi:10.1093/jnci/dji315
- 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. doi:10.1001/jama.2010.1672
- Mok TS, Leung TW, Lee SD, et al. A multi-centre randomized phase II study of nilotrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol*. 1999;44(4):307–311. doi:10.1007/s002800050982
- Mekky MA, Sayed HI, Abdelmalek MO, et al. Prevalence and predictors of occult hepatitis C virus infection among Egyptian patients who achieved sustained virologic response to sofosbuvir/daclatasvir therapy: a multi-center study. *Infect Drug Resist*. 2019;12:273. doi:10.2147/IDR.S181638
- Mekky MA, Abdel-Malek MO, Osman HA, et al. Efficacy of ombitasvir/paritaprevir/ritonavir/ribavirin in management of HCV genotype 4 and end-stage kidney disease. *Clin Res Hepatol Gastroenterol*. 2019;43(1):82–87. doi:10.1016/j.clinre.2018.08.003
- Elsherbiny NM, Rammadan M, Hassan EA, et al. Autoimmune hepatitis: shifts in gut microbiota and metabolic pathways among Egyptian patients. *Microorganisms*. 2020;8(7):1011. doi:10.3390/microorganisms8071011
- Hetta HF, Elkady A, Morsy KH, Mohamed IS, Ibrahim MA. Serum level of IL17a among cirrhotic hepatitis C virus infected patients with incidence of diabetes mellitus. *Egypt J Immunol*. 2017;24(1):79–88.
- Hetta HF, Khairy H, Ismail S. Circulating IL17A and IFN-gamma serum levels in cirrhotic hepatitis C virus infected patients with autoimmune thyroiditis. *Int J Curr Microbiol Appl Sci*. 2017;6(3):1972–1983. doi:10.20546/ijemas.2017.603.225
- Mehta M, Hetta HF, Abdel-Hameed EA, et al. Association between IL28b rs12979860 single nucleotide polymorphism and the frequency of colonic T reg in chronically HCV-infected patients. *Arch Virol*. 2016;161(11):3161–3169. doi:10.1007/s00705-016-3015-4
- Hetta HF, Mekky MA, Khalil NK, et al. Extra-hepatic infection of hepatitis C virus in the colon tissue and its relationship with hepatitis C virus pathogenesis. *J Med Microbiol*. 2016;65(8):703. doi:10.1099/jmm.0.000272
- Abdel-Hameed EA, Rouster SD, Ji H, et al. Evaluating the role of cellular immune responses in the emergence of HCV NS3 resistance mutations during protease inhibitor therapy. *Viral Immunol*. 2016;29(4):252–258. doi:10.1089/vim.2015.0093
- Pons F, Varela M, Llovet JM. Staging systems in hepatocellular carcinoma. *HPB*. 2005;7(1):35–41. doi:10.1080/13651820410024058
- Abd El-Baky RM, Hetta HF, Koneru G, et al. Impact of interleukin IL-6 rs-1474347 and IL-10 rs-1800896 genetic polymorphisms on the susceptibility of HCV-infected Egyptian patients to hepatocellular carcinoma. *Immunol Res*. 2020;68(3):118–125. doi:10.1007/s12026-020-09126-8
- Ma YS, Liu JB, Wu TM, Fu D. New therapeutic options for advanced hepatocellular carcinoma. *Cancer Control*. 2020;27(3):1073274820945975. doi:10.1177/1073274820945975
- Hetta HF, Mehta MJ, Shata MTM. Gut immune response in the presence of hepatitis C virus infection. *World J Immunol*. 2014;4(2):52–62. doi:10.5411/wji.v4.i2.52
- Shata MTM, Abdel-Hameed EA, Hetta HF, Sherman KE. Immune activation in HIV/HCV-infected patients is associated with low-level expression of liver expressed antimicrobial peptide-2 (LEAP-2). *J Clin Pathol*. 2013;66(11):967–975. doi:10.1136/jclinpath-2013-201581
- Zahran AM, Nafady-Hego H, Mansor SG, et al. Increased frequency and FOXP3 expression of human CD8+ CD25High+ T lymphocytes and its relation to CD4 regulatory T cells in patients with hepatocellular carcinoma. *Hum Immunol*. 2019;80(7):510–516. doi:10.1016/j.humimm.2019.03.014
- Hetta HF, Zahran AM, Mansor SG, Abdel-Malek MO, Mekky MA, Abbas WA. Frequency and implications of myeloid-derived suppressor cells and lymphocyte subsets in Egyptian patients with hepatitis C virus-related hepatocellular carcinoma. *J Med Virol*. 2019;91(7):1319–1328. doi:10.1002/jmv.25428

34. Zahran AM, Zahran ZAM, El-Badawy O, et al. Prognostic impact of toll-like receptors 2 and 4 expression on monocytes in Egyptian patients with hepatocellular carcinoma. *Immunol Res*. 2019;67(2-3):157–165.
35. Abd Allah NH, Tawfeek HM, John J, Hetta HF. Nanomedicine as a future therapeutic approach for hepatitis C virus. *Nanomedicine*. 2019;14(11):1471–1491. doi:10.2217/nmm-2018-0348
36. Chaturvedi VK, Singh A, Dubey SK, Hetta HF, John J, Singh M. Molecular mechanistic insight of hepatitis B virus mediated hepatocellular carcinoma. *Microb Pathog*. 2019;128:184–194. doi:10.1016/j.micpath.2019.01.004
37. Zahran AM, Ashmawy AM, Rayan A, Elkady A, Elsherbiny NM, Hetta HF. Frequency and implications of natural killer and natural killer T cells in hepatocellular carcinoma. *Egypt J Immunol*. 2018;25(2):45–52.
38. Hetta H, Elkady A, Tohamy T, Regulatory BM. B cells: key players in hepatocellular carcinoma progression. *Gastroenterol Hepatol Open Access*. 2016;5(2):00136. doi:10.15406/ghoa.2016.05.00136
39. Hetta HF, Mekky MA, Khalil NK, et al. Association of colonic regulatory T cells with hepatitis C virus pathogenesis and liver pathology. *J Gastroenterol Hepatol*. 2015;30(10):1543–1551. doi:10.1111/jgh.12936
40. Zhang L, Ding J, Li HY, Wang ZH, Wu J. Immunotherapy for advanced hepatocellular carcinoma, where are we? *Biochim Biophys Acta Rev Cancer*. 2020;1874:188441. doi:10.1016/j.bbcan.2020.188441
41. Zahran AM, Hetta HF, Rayan A, et al. Differential expression of Tim-3, PD-1, and CCR5 on peripheral T and B lymphocytes in hepatitis C virus-related hepatocellular carcinoma and their impact on treatment outcomes. *Cancer Immunol Immunother*. 2020;1–11.
42. Gupta N, Verma RK, Prinja S, Dhiman RK. Cost-effectiveness of sorafenib for treatment of advanced hepatocellular carcinoma in India. *J Clin Exp Hepatol*. 2019;9(4):468–475. doi:10.1016/j.jceh.2018.10.003
43. Sasse A, Carmo R. P-239 Sorafenib for advanced hepatocellular carcinoma (HCC) in the public health setting in Brazil: a cost-effectiveness analysis. *Ann Oncol*. 2019;30(Supplement_4):mdz155.238. doi:10.1093/annonc/mdz155.238
44. Zhang P, Yang Y, Wen F, et al. Cost-effectiveness of sorafenib as a first-line treatment for advanced hepatocellular carcinoma. *Eur J Gastroenterol Hepatol*. 2015;27(7):853–859. doi:10.1097/MEG.0000000000000373
45. Feng F, Jiang Q, Jia H, et al. Which is the best combination of TACE and Sorafenib for advanced hepatocellular carcinoma treatment? A systematic review and network meta-analysis. *Pharmacol Res*. 2018;135:89–101. doi:10.1016/j.phrs.2018.06.021
46. Hassan EA, Ahmed EH, Nafee AM, El-Gafary N, Hetta HF, El-Mokhtar MA. Regulatory T cells, IL10 and IL6 in HCV related hepatocellular carcinoma after transarterial chemoembolization (TACE). *Egypt J Immunol*. 2019;26(1):69–78.
47. Ma X, Li RS, Wang J, et al. The therapeutic efficacy and safety of compound kushen injection combined with transarterial chemoembolization in unresectable hepatocellular carcinoma: an update systematic review and meta-analysis. *Front Pharmacol*. 2016;7:70. doi:10.3389/fphar.2016.00070
48. Xie H, Yu H, Tian S, et al. What is the best combination treatment with transarterial chemoembolization of unresectable hepatocellular carcinoma? A systematic review and network meta-analysis. *Oncotarget*. 2017;8(59):100508–100523. doi:10.18632/oncotarget.20119
49. Qin S, Cheng Y, Liang J, et al. Efficacy and safety of the FOLFOX4 regimen versus doxorubicin in Chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the EACH study. *Oncologist*. 2014;19(11):1169–1178. doi:10.1634/theoncologist.2014-0190
50. Qin S, Zhang X, Guo W, et al. Prognostic nomogram for advanced hepatocellular carcinoma treated with FOLFOX 4. *Asian Pac J Cancer Prev*. 2017;18(5):1225–1232.
51. Zaanani A, Williet N, Hebbar M, et al. Gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma: a large multicenter AGEO study. *J Hepatol*. 2013;58(1):81–88. doi:10.1016/j.jhep.2012.09.006
52. 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. doi:10.1002/cncr.22532
53. Taïeb J, Bonyhay L, Golli L, et al. Gemcitabine plus oxaliplatin for patients with advanced hepatocellular carcinoma using two different schedules. *Cancer*. 2003;98(12):2664–2670. doi:10.1002/cncr.11869
54. Liu L, Zheng YH, Han L, Qin SK. Efficacy and safety of the oxaliplatin-based chemotherapy in the treatment of advanced primary hepatocellular carcinoma: a meta-analysis of prospective studies. *Medicine*. 2016;95(40):e4993. doi:10.1097/MD.0000000000004993

Cancer Management and Research

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>

Dovepress

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.