

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

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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

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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	PIAF	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 d1and2, FU 400mg/m ² then 600mg/m ² over 22hr every 2 wks	Doxorubicin 50mg/m ² every 3 weeks	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	Doxorubicin 60 mg/m ² every 21 days + sorafenib 400mg BID daily	60 mg/m ² every 21 days	60mg/m ² d1 every 3 weeks	725 mg/m ² over 5 days every 3 weeks
Number in each arm	26	26	184	187	222	223	94	94	47	49	18	36
Main inclusion criteria	● No previous therapy ● Not a candidate for surgery or local treatment		● 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		● KPS ≥ 60% ● CLIP scores≤3 ● Adequate liver function LVEF ≥50%		● Unresectable or metastatic cancer ● Total bilirubin ≤ 1.75 mg/dl ● Uncontrolled ascites		● No prior chemotherapy LVEF ≥45%		● KPS≥ 70 ● Bilirubin ● No prior CTX within 4 weeks only	
Main exclusion criteria	● Renal failure on dialysis ● CHF NYHA > class II ● Active CAD ● Metastatic brain cancer ● Concurrent Cancer		● Previous oxaliplatin or doxorubicin treatment except adjuvant more than 12ms ● Previous liver transplant ● CNS metastasis ● Serious illness		● Resectable liver lesion Transplant candidate (included later) ● Prior doxorubicin or liposomal doxorubicin ● Severe intercurrent illness		● Any history of cancer except NM skin cancer ● Bone & brain mets ● Prior CTX ● Serious illness		● Prior TA chemoembolization ● Psychological or social problem ● Fibrolamellar or mixed histology		● Bilirubin >3 mg/dL, AST or ALT >5.0 ´ upper normal limit or albumin <3 g/d ● Uncontrolled ascites ● Another malignancy with5 years of randomization	

(Continued)

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% HBV 26.1% History of Alcoholism 29.3%	HCV 43% HBV 18.4% 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	Sorafenib	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	1.55m
	p < 0.005, HR 2.708		p < 0.001, HR 0.62		p = 0.709				p = 0.006, HR: 0.45			
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		p = 0.07, HR 0.8		p = 0.0068, HR 0.753		p = 0.83, HR 0.97		p = 0.006, HR 0.49		p = 0.9843	
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

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

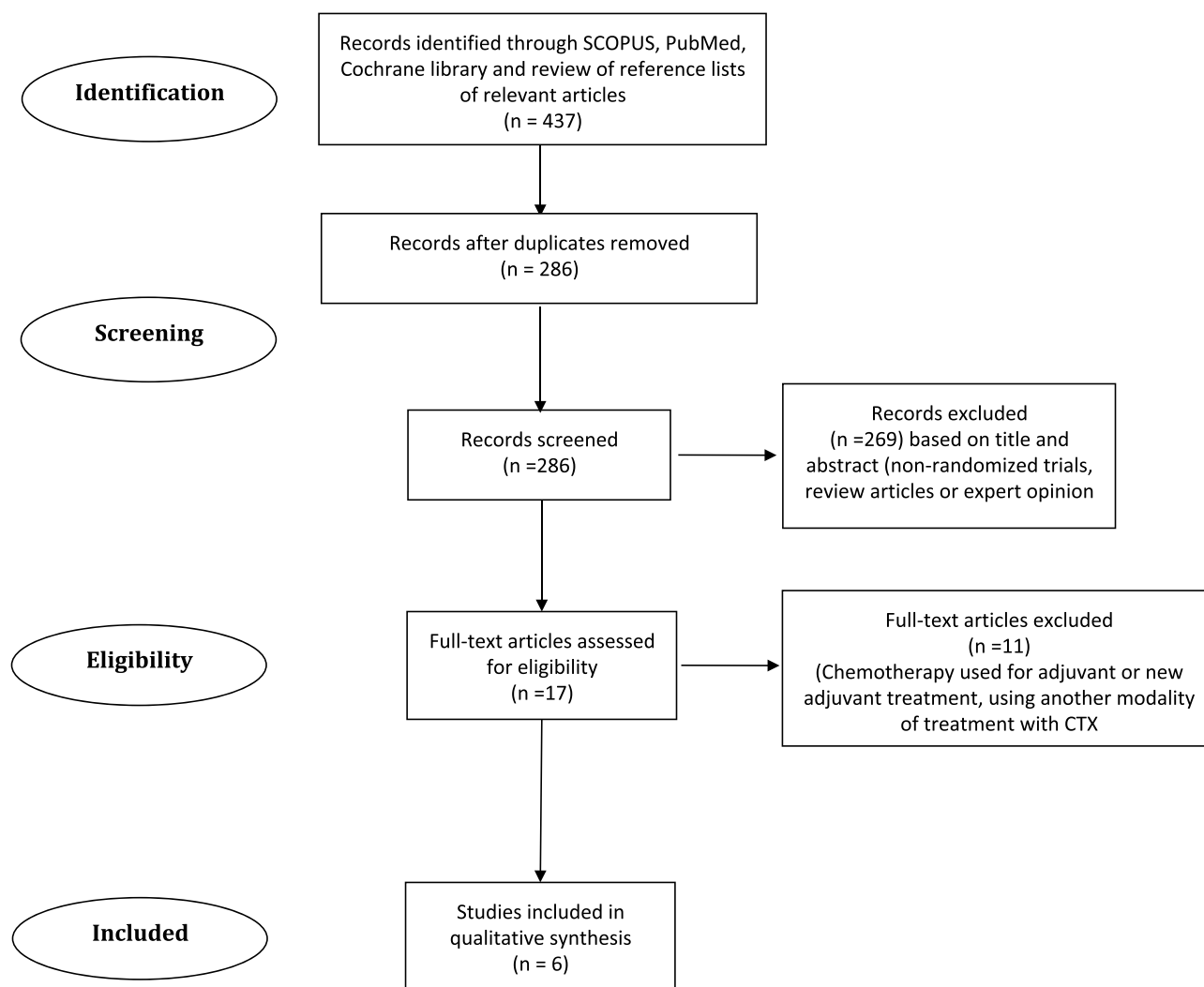


Figure 1 Flow chart of study selection.

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.

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Disclosure

The authors declare no conflicts of interest.

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