CHAPTER 1
INTRODUCTION

1.1 Objective

To assess the efficacy of cytotoxic chemotherapy compared with sorafenib in improving the survival rates of advanced hepatocellular carcinoma patients.

1.2 Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is sixth most common cancer worldwide and the third most common cause of death from cancer. In Asian countries, approximately three-fourth of cases occur due to high prevalence of chronic infection with HBV.[1,2]

Recent study in Malaysia by Norsa'adah et al showed that majority of HCC cases were diagnosed as stage 3A with overall median survival time 1.9 months, meanwhile Malaysia Cancer Registry showed that 62% of HCC were presented in stage 4 of disease. This short survival time might be due to the facts that most of the patients (83% of the patients) in this study received no treatment at all.[3]

According to the guidelines issued by Asian Pasific Association for the Study of the Liver (APASL) on hepatocellular carcinoma, patients with advanced stage of hepatocellular carcinoma defined by extrahepatic metastasis or main portal vein tumor thrombus with Child Pugh classification A or B should receive sorafenib or systemic therapy trial.[4] This recommendation in accordance with Barcelona Clinic Liver Cancer (BCLC) recommendation that suggests using new agents such as targeted therapy agent, sorafenib in advanced hepatocellular carcinoma patients.[1,4]

Sorafenib works by targeting specific receptors such as RAF kinase, vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factors receptors (PDGFR), c-kit, Flt-3 and RET. When compared to placebo, sorafenib increases overall survival patients with advanced hepatocellular carcinoma.[1]

Regardless of its efficacy in improving survival of advanced hepatocellular carcinoma patients, Sorafenib is an expensive new agent and

not covered by national health insurance in Indonesia. In addition, other molecular targeted therapy agents such as bevacizumab and sumatinib are not available yet so most of the patients with advanced hepatocellular carcinoma in Indonesia do not receive any treatment and have low survival rate.

Another treatment option for patients with advanced hepatocellular carcinoma is systemic cytotoxic chemotherapy. It has been used before sorafenib became available but now its role was limited due to its myelosupressive toxicity. Regardless of that matter, considerable number of patients in Korea are taking cytotoxics as a first line agents for advanced hepatocellular carcinoma due to the same problem that we encounter in Indonesia.[5]

Based on this circumstances, we would like to assess the role of cytotoxic chemotherapy in the era of targeted therapy by comparing the efficacy of cytotoxic chemotherapy with sorafenib in improving the survival rates of advanced hepatocellular carcinoma patients using evidence based case report (EBCR).

CHAPTER 2
CASE RESUME

2.1 Case Resume

Male 59 years old came to the outpatient clinic with chief complain enlarged stomach since six months ago. Enlarged stomach was accompanied by pain on the right quadran of abdomen and nausea. There is no fever, hematemesis nor melena. His weight was loss up to five kilograms in six months. He has no history of hepatitis before. There is no history of hepatitis nor cancer in his famiy. He did not smoke, did not has any tattoo, did not use intravenous drug and did not has history of blood tranfusion.

His vital sign was stable and from the physical examination we found palmar eritema, spider naevi on his chest, enlarged abdomen with hepatomegali two fingers below the costal arch, splenomegali Schuffner III and shifting dullness sign positive.

The laboratory result showed anemia with Hb 11.5 g/dL and thrombocytopenia with platelet count 122.000/µL. Liver function test and bilirubin level was elevated (AST 222 U/L, ALT 85 U/L, total bilirubin 2.15 mg/dL with direct bilirubin 1.31 mg/dL). Albumin 3.53 g/dL, with PT 14.6 seconds (control 11.3 seconds) and APTT 39.2 seconds (control 29.7 seconds). HBsAg was reactive and anti HCV total non reactive.

CT scan abdomen with contrast showed hepatomegali with lobulated tip and poorly defined hipodensed mass with early arterial enhancement and early wash out with delayed enhancement on vein phase sized 10.3 x 8.7 cm in fifth and eight segments and 5.4 x 4.7 cm in the sixth segment of the liver. There are also thrombus in the main, right and most of the left portal vein and splenomegali without dilatation of the splenic vein.

He was diagnosed with advanced hepatocellular carcinoma Bacelona Clinic Liver Cancer classification stage C and liver cirrhosis Child Pugh B caused by hepatitis B with ascites, hyperbilirubinemia and elevated transaminase level.

We planned to give sorafenib for the hepatocellular carcinoma but it is not covered by national health insurance. Due to the high cost, it was not affordable by the patient so in the end he did not receive any treatment for the cancer.

There is another option of treatment for advanced hepatocellular carcinoma by using cytotoxic chemotherapy and it has been used before when Sorafenib was not available yet. We consider to use cytotoxic chemotherapy for this patient but we need more data regarding its efficacy compared to sorafenib in improving the survival rates of advanced hepatocellular carcinoma patients.

2.2 Clinical Question

“ Is cytotoxic chemotherapy effective in improving the survival rates of advanced hepatocellular carcinoma patients compared to sorafenib?”

CHAPTER 3
METHODS

3.1 Search The Evidence

P : adult, advanced hepatocellular carcinoma patients

I : cytotoxic chemotherapy

C : sorafenib

O : survival rate

We searched Pubmed and Cochrane library database on August 12th, 2015 using the terms : (((((survival rate) OR prognosis)) AND ((sorafenib) OR targeted therapy)) AND ((((hepatoma) OR hepatocellular carcinoma) AND advanced) OR end stage)) AND ((systemic chemotherapy) OR cytotoxic chemotherapy). Our search produced 144 results from PubMed and 3 results from Cochrane library. We looking only for trials with human subjects and found 133 results from Pubmed and 3 results from Cochrane. In order to attain the newest evidence, we limit our search to articles that was published within five years back from now (2010-2015). We found 102 results from Pubmed and 3 results from Cochrane. Next, we screened the abstract for trials that only compare cytotoxic chemotherapy with sorafenib and got 4 results from Pubmed and 0 results from Cochrane. We did not get the full text on one of those articles so 3 articles remain. We read the full text of these articles and decided all of them can be used in the next process.

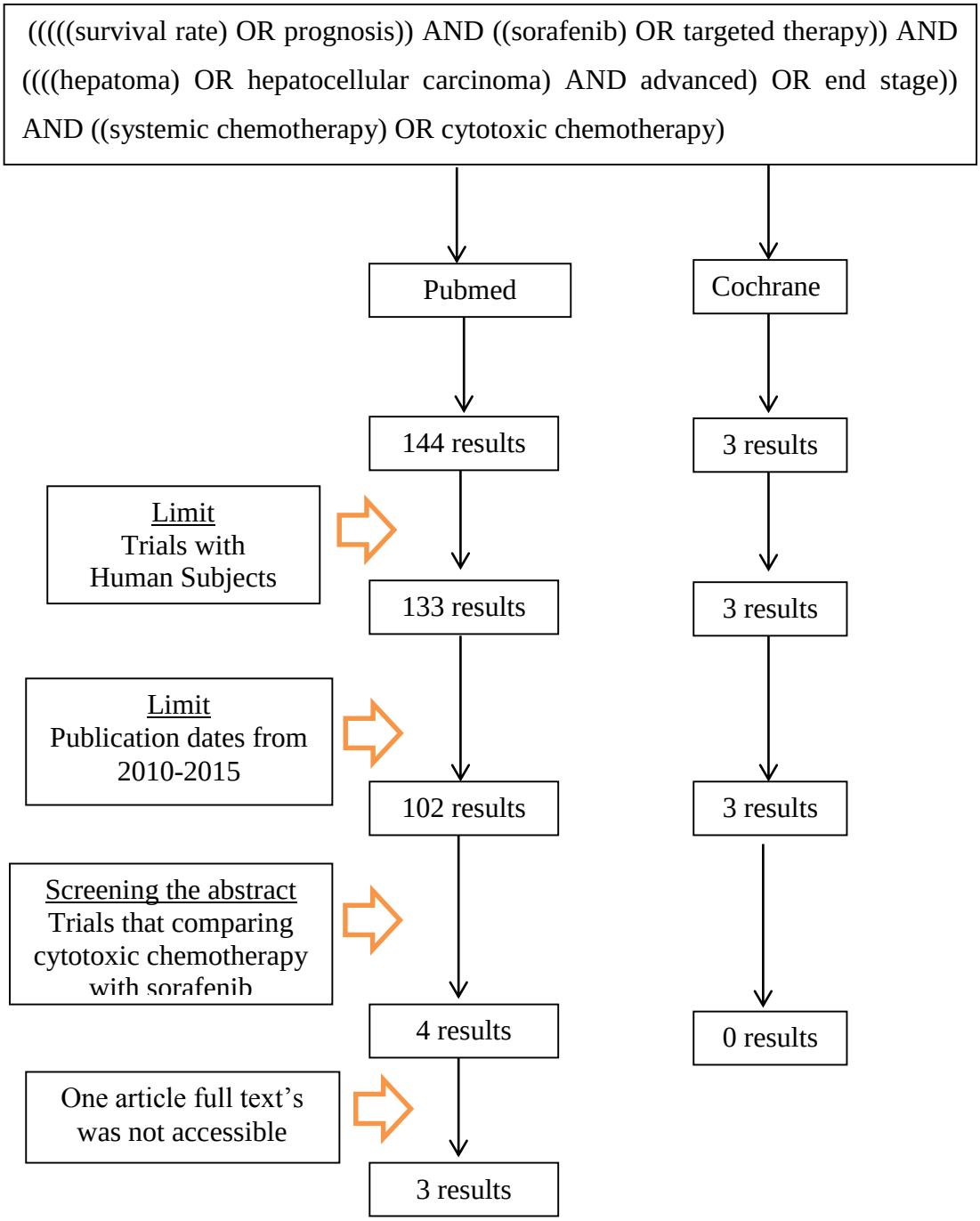

Figure 3.1 Flowchart of Conducted Search

3.2 Appraise The Evidence

According to Oxford Centre for Evidence-based Medicine-Levels of Evidence, the best and highest level of evidence of therapeutic type clinical question is systematic review of randomized controlled trials (RCTs) [Level 1a]. The second best level of evidence is individual RCT with narrow confidence interval [Level 1b], followed by a systematic review of cohort studies [Level 2a], individual cohort study [Level 2b], systematic review of case-control studies [Level 3a], individual case-control study [Level 3b], case series [Level 4] and expert opninion [Level 5].[6] After searching PubMed and Cochrane to answer the clinical questions, we found only 3 articles with 1 RCT and the others were individual cohort studies.

We appraised the scientific evidence of these articles using guidance from Centre for Evidence-Based Medicine : Critical Appraisal for Therapy Articles and also Critical Appraisal Skills Programme (CASP).[7,8]. The result was shown below.

Table 3.2 Critical Appraisal of Randomized Controlled Trial

Appraisal questions	Abdel-Rahman et al (2013)[9]
Validity	
1.Was the assignment of patients to treatment randomised?	Yes
2.Were the groups similar at the start of the trial?	No
3.Aside from the allocated treatment, were groups teated equally?	Yes
4.Were all patients who entered the trial accounted for?-and were they analysed in the groups to which they were randomised?	Yes
5.Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	No

Importancy	
6.Is the size effect practically relevant?	Yes
7.How precise is the estimate of the effect? Were confidence intervals given?	Yes
Applicability	
8.Is my patient so different to those in the study that the results canot apply?	No
9.Is the treatment feasible in my setting?	Yes
10.Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?	Yes
Level of Evidence*	1b

*Level of Evidence obtained from Centre for Evidence Based Medicine, University of Oxford (available at : http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/)

Table 3.3 Critical Appraisal of Cohort Studies

Appraisal Questions	Lee et al (2012)[5]	Yoon et al (2014)[10]
Validity		
1.Did the study address a clearly focussed issue?	Yes	Yes
2.Was the cohort recruited in an acceptable way?	Yes	Yes
3.Was the exposure accurately measured to minimise bias?	Yes	Yes
4.Was the outcome accurately measured to minimise bias?	Yes	Yes
5aHave the authors identified all important confounding factors?	Yes	Yes
5b.Have they taken account of the confounding factors in the design and/or analysis?	Yes	Yes
6a.Was the follow up of subjects complete enough?	Yes	Yes

6b.Was the follow up of subjects long enough?	Yes	Yes
Importancy		
7.What are the results of this study?	Cytotoxic chemotherapy is not inferior compared with sorafenib	Cytotoxic chemotherapy is not inferior compared with sorafenib
8.How precise are the results?	Not precise enough	Not precise enough
9.Do you believe the results?	Cant tell	Cant tell
Applicability		
10.Can the results be applied to the local population?	Yes	Yes
11.Do the result of this study fit with other available evidence?	Yes	Yes
12.What are the implications of this study for practice?	Consider using cytotoxic cehmotherapy	Consider using cytotoxic cehmotherapy
Level of evidence*	2b	2b

*Level of Evidence obtained from Centre for Evidence Based Medicine, University of Oxford (available at : http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/)

After apprasing those articles, we found that both of the cohort studies by Lee and Yoon et al were valid but might not important enough due to statistically insignificant results. Meanwhile, RCT by Abdel-Rahman et al might less valid due to the differences between the two study groups and neither of the patients nor clinicians were blinded regarding the treatment.

CHAPTER 4

RESULTS

In this evidence based case report, we try to answer if cytotoxic chemotherapy is effective in improving the survival rates of advanced hepatocellular carcinoma patients compared to sorafenib. We found one RCT and two cohort studies that were focused on answering this question. Results of these studies have been summarized in table shown below.

Table 4.1 Summary of RCT by Abdel Rahman et al (2013)[9]

Outcome	Sorafenib	Fluoropyrimidines	Hazard ratio	P value
Progression-free survival (mo)				
Median	6	4	2.708 (1.34-5.43)	0.005
95% CI	3.2-8.7	3.6-4.3		
Overall survival (mo)				
Median	7.05	5.07	2.36 (1.174-4.74)	0.016
95% CI	5.58-8.43	4.65-5.48		
Levels of response				
Complete response	1 (3%)	0		0.21
Partial response	3 (11.5%)	1 (3%)		0.12
Stable disease	16 (61%)	14 (53.8%)		0.23

Table 4.2 Summary of Cohort Study by Lee et al (2012)[5]

Outcome	Sorafenib (*N*=44)	Chemotherapy (*N*=129)	P value
Overall survival (mo)			0.105
Median	23.0	43.6	
95% CI	8.1–37.9	34.0–53.2	
1-yr survival rate (%)	13 (29.5%)	47 (36.4%)	0.407
Progression free survival (mo)			0.138
Median	11.1	12.4	
95% CI	6.4–15.8	8.1–16.7	
Level of response (%)			0.070
Complete	0 (0)	0 (0)	
Partial	1 (2.3)	8 (6.2)	
Stable	22 (50.0)	48 (37.2)	
Progressive disease	18 (40.9)	63 (48.3)	
Not assessable	3 (6.8)	10 (7.8)	
DCR, n (%)	23 (52.3)	56 (43.4)	0.308
Median cycle (range)	2.4 (0.5–17)	3 (1–13)	
Dose reduction, n (%)	19 (43.2%)	15 (11.5%)	
Treatment delay, n (%)	16 (36.4%)	25 (19.3%)	

Table 4.3 Summary of Cohort Study by Yoon et al (2012)[10]

Outcome	Sorafenib	Chemotherapy	Hazard ratio	P value
Progression-free survival (mo)				
Median	3.2	5.9		0.07
95% CI	2.2-4.3	3.6-8.7		
Overall survival (mo)				
Median	7.2	11.2	1.474 (0.36-3.6)	0.10)
95% CI	5.6-8.8	8.1-14.2		
Best response rates				
Complete response	2 (2.6%)	0		0.55
Partial response	8 (10.3%)	2 (1.43%)		0.66
Stable disease	25 (32.1%)	9 (64.3%)		0.03
Disease progession	31 (39.7%)	3 (21.4%)		0.24
Not evaluable	12 (15.4%)	0		0.12
Objective response rates	10 (12.8%)	2 (14.3%)		0.29
Disease control rates	35 (44.9%)	11 (78.6%)		0.05

From those result, we can see that overall median survival was significantly longer in the sorafenib group than in the capecitabine group. The response rates also better in the sorafenib group.

This result was contradictive to Lee et al studies that showed median overall survival with sorafenib was lower than chemotherapy group. The median progression-free survival also did not differ significantly between those two groups. Consistent with those results, Yoon et al showed that cytotoxic chemotherapy was better than sorafenib group not only in overall survival but also in progression-free survival. Unfortunately, these results were not statistically significant (P value > 0.05).

Regarding response rates, Abdel-Rahman and Yoo et al results showed that sorafenib was better than chemotherapy group, while Lee et al results showed contradictively. All of these results were also not statistically significant (P value > 0.05).

General cytotoxic chemotherapy showed significantly higher frequencies of neutropenia and thrombocytopenia than sorafenib, although sorafenib was associated with high rates of dermatologic toxicity such as hand-food reaction, rash and pruritis (P value < 0.005).[5,10] Capecitabine also significantly induced thrombocytopenia compared with sorafenib (P value 0.001), but overall adverse events were higher in sorafenib group (P value 0.039).[9]

CHAPTER 5
DISCUSSION

Based by Asian Pacific Association for the Study of the Liver (APASL) consensus recommendations on hepatocellular carcinoma, advanced stage hepatocellular carcinoma was treated by sorafenib or systemic therapy trial.[1] This recommendation was consistent with American Association for the Study of Liver Diseases (AASLD) and The Barcelona Approach for treatment of hepatocellular carcinoma.[11,12]

Both AASLD and The Barcelona Approach do not recommend using cytotoxic chemotherapy anymore in their guidelines, meanwhile APASL still considered using cytotoxic drugs in highly selected patients whose general and hepatic conditions are adequate.[1]

Sorafenib was recommended for advanced stage patients with hepatocellular carcinoma and had a statistically significant effect on prolonging overall survival.[1,13,14] It is a molecular targeted drug, multityrosine kinase inhibitor, targets angiogenic VEGFR-1, -2, and -3; PDGFR-β and tumorigenic RET, Flt-3, and c-Kit receptors. It potently inhibited cellular proliferations, Raf/MEK/ERK signlaing and induced apoptosis.[13]

Systemic cytotoxic chemotherapy for hepatocellular carcinoma has been associated with low response rates and no survival benefit, partly because hepatocellular carcinoma is a chemotherapy-resistant tumor, due to the expression of the multi-drug resistance gene MDR-1- and partly due to the underlying liver cirrhosis in most patients, which prevents the administration of full dosage of many drugs.[15] Thats why, after sorafenib has been established as the standard treatment in advanced hepatocellular carcinoma patients, the role of cytotoxic chemotherapy is limited.

However, sorafenib has not been supported by national health insurance in some Asian countries, including Indonesia and it is quite costly relative to available cytotoxic drugs. Based on that issue, cytotoxic drugs may have role in improving the survival rates of advanced hepatocellular carcinoma patients in the era of targeted therapy.

Lee et al study used doxorubicin-nd/or platinum based-mostly doublet (fluorouracil plus doxorubicin or fluorouracil plus platinum) or triplet (fluorouracil plus doxorubicin and platinum) agents repeated every three or four weeks according to their institutional protocol. Most of the patients used 5FU 1000 mg/m2 D1-3 and Cisplatin 60 mg/m2 or Carboplatin AUC 5 D1 repeated eevry 4 weeks (72.1%). Sorafenib was given at 400 mg twice-daily doses in 4-week cycles. Median overall survival was better in chemoterapy group (43.6 months vs 23.0 months) with P value 0.105. Progression free survival did not differ significantly in both sorafenib and chemotherapy group.

Lee et al study result showed cytotoxic chemotehrapy still has a role in the era of targeted agent and can be better than sorafenib regarding overall survival and progression free survival. However, those results did not statistically significant.

Patients in Lee at al study were not equally distributed by baseline AFP level, which is a major prognostic factor with hepatocellular carcinoma. Most of the patients in the sorafenib group have AFP level ≥400 ng/mL (24 of 44; 54.5%). Meanwhile, most of the patients in the chemotherapy group have AFP level <400 ng/mL (80 of 128; 62.5%). Baseline AFP <400 ng/mL was a favorable parameters relative to overall survival and progression free survival.[5] There is also no standardization of chemotherapy regimens that were used. Lee et al conclude that cytotoxic chemotherapy is not inferior for some patients with advanced HCC and the greatest therapeutic benefit may in the setting of good performance status, no macrovascular invasion and low level of AFP.

Yoon et al study used adriamycin, cisplatin and capecitabine for the cytotoxic chemotherapy group. Doxorubicin 60 mg/m2 and cisplatin 60 mg/m2 were given on day 1 with capecitabine at a dose of 1000 mg/m2 twice daily from day 1 through day 14. This regimen was repeated every 4 weeks. Sorafenib was given a dose 400 mg twice daily and the treatment period was divided into 6-week cycles.

Yoon et al study result showed that cytotoxic chemotherapy was better than sorafenib group not only in overall survival (11.2 months vs 7.2 months) but

also in progression-free survival (5.9 months vs 3.2 months). However, these results were not statistically significant (P value > 0.05).

The shorter overall survival survival in the sorafenib compared with cytotoxic chemotherapy and also in the other sorafenib trials such as Sorafenib HCC Assessment Randomized Protocol trial might be caused by a large number of patients with impaired liver function, which reached 23.1% to 28.6% in both sorafenib and chemotherapy group. There were also patients with aggresive tumor characteristics such as the presence of macroscopic vessel invasion and distant metastases in both the sorafenib and the cytotoxic chemotherapy groups in their study. The efficacy of sorafenib can be limited by liver function, performance status and the aggressivenes of tumor characteristics.

The essential duration of the treatment in the sorafenib group as maintenance in Yoon et al study was >15 days, which is rather short for the evaluation of the biological effects of sorafenib treatment. The mean duration of treatment and the number of the treatment cycles were much shorter in the sorafenib group that may be caused by adverse events.

Another limitation in Yoon et al study is the small number of patients in the systemic cytotoxic chemotherapy group compared with sorafenib group (14 patients vs 78 patients) and not a head to head comparison of sorafenib and cytotoxic chemotherapy just like Lee et al study. Nevertheless, baseline characteristics for sorafenib and chemotherapy groups including AFP level was not different significantly (P value < 0.05).

Yoon et al conclude that efficacy of systemic cytotoxic chemotherapy was not inferior to that of the sorafenib group when overall survival, progression-free survival and disease control rates were compared.

Abdel-Rahman et al study used capecitabine orally 1000 mg/m2 twice daily for 14 days as part of a 21-day cycle while sorafenib was given 800 mg daily. Overall median survival was significantly longer in the sorafenib group than in the capecitabine group (7.05 vs 5.07 months, P value < 0.016). The same results applied to progression free survival and response rates.

Abdel-Rahman conclude that sorafenib is more effective in improving survival compared with capecitabine for patients with advanced hepatocellular

carcinoma. However, there is different baseline characteristics of patients in sorafenib and capecitabine group such as Child-Pugh class (36% vs 58% for Child-Pugh class Late B; P value 0.04) and extrahepatic spread (23% vs 65%; P value 0.001). It showed that patients in capecitabine group were in more advanced stage of hepatocellular carcinoma than those in sorafenib group.

All of the studies showed that cytotoxic chemotherapy has more serious adverse events such as neutropenia and thrombocytopenia although Yoon et al mentioned that sorafenib was more intolerable than cytotoxic therapy in their study.

CHAPTER 6
CONCLUSION

Cytotoxic chemotherapy is not inferior to sorafenib in improving the survival rates of advanced hepatocellular carcinoma patients, depending on what regimens have been used.