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Combination of oxaliplatin and S-1 *versus* sorafenib alone in patients with advanced hepatocellular carcinoma

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Sorafenib and conventional systemic cytotoxicity chemotherapy are currently being used in parallel for the patients with advanced hepatocellular carcinoma (HCC). While sorafenib has been proven to improve the prognosis in patients with this malignant disease, however, the outcome of other newly developed systemic chemotherapeutic regimens remains controversial. We evaluated the outcome and safety of patients treated with the SOX regimen (oxaliplatin + S-1) and those treated with sorafenib in a single-center cohort. This retrospective study involved a total of 46 patients with advanced HCC, 22 of which were treated with SOX regimen (oxaliplatin [130 mg/m^2] on day 1 and S-1 [80 mg/m^2/day] on day 1–14, every 3 weeks), and 24 were daily treated with sorafenib (400 mg, b.i.d.). The median progression-free survival was 3.6 months (95% confidence interval [CI], 1.7 to 5.6) with SOX and 1.7 months (95% CI, 1.5 to 1.9) with sorafenib, respectively ($P = 0.444$). The median overall survival in SOX and sorafenib group was 7.6 months (95% CI, 4.3 to 10.9) and 4.7 months (95% CI, 2.7 to 7.3), respectively ($P = 0.246$). Response rate was 22.2% with SOX and 5.6% with sorafenib, respectively ($P = 0.154$). The frequent side effects in SOX-treated patients were thrombocytopenia, elevation of transaminase levels and neuropathy, whereas hand–foot syndrome, diarrhea and pruritus were common in sorafenib-treated patients. These preliminary results suggest that the SOX regimen may serve as an effective treatment for patients with advanced HCC, and the treatment-related toxicities were generally well-tolerated.

1. Introduction

The progressive development of hepatocellular carcinoma (HCC) is attributable to multiple pathologic causes, including chronic infections of hepatitis viruses, alcoholism, nonalcoholic steatohepatitis, autoimmune hepatitis, primary sclerosing cholangitis and biliary cirrhosis, and some of inherited disorders like hemochromatosis and α-1-antitrypsin (α1AT) deficiency. The prevalence of hepatitis-B virus (HBV) and hepatitis-C virus (HCV) infections contributes to the high incidence of hepatocellular carcinoma (HCC)) in Asia, which currently is the third most common cancer in this area, and 55% of HCC cases throughout the world are estimated to occur in China (Yuen et al. 2009; Jemal et al. 2011). Approximately 70% of patients with HCC present with locally advanced or metastatic disease (Taieb et al. 2006; Rougier et al. 2007) and can receive only palliative treatment. Transarterial chemoembolization was shown to improve survival (Llovet et al. 2002; Lo et al. 2002), but is ineffective for vascular invasion or extrahepatic spreading (Bruix and Sherman 2005).

Previous clinical trials showed that the novel cytotoxic agents used for the systemic treatment of advanced HCC, such as gemcitabine, capecitabine and oxaliplatin, exhibited considerable efficacy with tolerable toxicities (Zhu et al. 2006; Lee et al. 2009). A phase-III study in East Asian patients with advanced HCC treated with FOLFOX4 chemotherapy (i.e., folinic acid, 5-fluorouracil [5-FU] and oxaliplatin) showed a significantly increased response rate (RR) and progression-free survival (PFS), and led to a trend towards longer overall survival (OS) than doxorubicin (Qin et al. 2013). Therefore, the chemotherapy with oxaliplatin and 5-FU are more preferable compared with doxorubicin for advanced HCC.

S-1 is an oral fluoropyrimidine and a novel 5-FU analog containing tegafur (a metabolically activated prodrug of 5-FU) and two biochemical modulators for 5-FU. 5-Chloro-2,4-dihydroxypyridine enhances the pharmacological actions of 5-FU by potently inhibiting its degradation by dihydropyrimidine dehydrogenase (Jiang et al. 1997; Ikeguchi et al. 2001). Potassium oxonate is localized in the mucosal cells of the gastrointestinal (GI) tract after oral administration. It reduces the incidence of GI toxicities by suppressing the activation of 5-FU in the GI tract. As compared with 5-FU, S-1 shows a better anti-tumor activity, lower toxicity, and more convenient administration. Phase-I/II studies revealed that when applied for the treatment of HCC at the recommended dose of 80 mg/m^2/day, S-1 exhibited promising efficacy and tolerable toxicity (Furuse et al. 2010).

Table 1: Patient characteristics at baseline

Characteristic	Number of patients		*P value*
	sorafenib	SOX[a]	
Gender			
Male	20	20	0.105
Female	4	2	
Age (years)			
Median (range)	47 (29-81)	46 (35-66)	0.574
Performance status (ECOG)[b]			
0	9	14	
1	14	7	0.103
2	1	1	
Child-Pugh class			
A	20	14	0.129
B	4	8	
Etiology of liver disease			
HBV infection	17	18	
HCV infection	0	0	0.338
No liver disease	7	4	
Underlying cirrhosis			
Yes	15	13	0.813
No	9	9	
Extra-hepatic metastasis			
Yes	9	18	0.037
No	15	4	
AFP[c] parameter			
$\geq$ 400 ng/ml	10	9	0.958
$<$ 400 ng/ml	14	13	

a, SOX, Oxaliplatin plus S-1; **b**, ECOG, Eastern Cooperative Oncology Group; **c**, AFP, alpha-fetoprotein

On the other hand, sorafenib has shown to prolong OS in patients with unresectable or metastatic HCC and therefore has been established as a standard treatment for advanced HCC (Llovet et al. 2008; Cheng et al. 2009). In the meanwhile, a substantial portion of the patients with advanced HCC is still being treated with systemic cytotoxic chemotherapy. Several newly developed drugs, such as oxaliplatin and S-1, and novel combination regimens have emerged (Asghar and Meyer 2012), however, the outcome of these chemotherapeutic programs has not yet been elucidated appropriately in compare with that of sorafenib. Since a head-to-head comparison of the chemotherapy with oxaliplatin plus S-1 and sorafenib alone has not yet been carried out, we retrospectively evaluated the efficacy and safety of a SOX regimen (oxaliplatin + S-1) *versus* sorafenib in advanced HCC.

2. Investigations and results

2.1. Patient characteristics

The patient characteristics are shown in Table 1. Twenty-two patients were treated with SOX and 24 patients with sorafenib from January, 2011 to March, 2013. Thirty-five patients (76%, 35/46) had HBV infection. Comparison of the clinical and demographic characteristics of patients in the two treatment arms revealed no significant differences in the distribution of baseline features (Table 1), except that extrahepatic spreading was more commonly observed in the SOX group ($P = 0.037$).

2.2. Tumor response

Twenty-two patients in the SOX group in total completed 61 cycles of chemotherapy, with a median of two cycles (range, 1 to 6). The average dose intensities were 90% for S-1 and oxaliplatin. Tumor response could be evaluated in 18 patients. Among the four patients in whom tumor response could not be evaluated, three patients received traditional Chinese medicine between the first and second cycle of chemotherapy, the other patient was lost to follow-up after two cycles of chemotherapy before evaluation of tumor response. In these 18 patients, no patient achieved a complete response (CR), but four patients (22.2%, 4/18) achieved a partial response (PR), seven patients had stable disease (SD) (38.9%, 7/18) and seven patients had progressive disease (PD) (38.9%, 7/18). In the sorafenib group, 24 patients completed 80 cycles of treatment in total, with a median of 1.8 cycles (range, 1 to 25). The average dose intensities were 95% for sorafenib. Four patients were lost to follow-up and two patients died (neither death was treatment-related) before response evaluation. One patient in the remaining 18 patients achieved a PR (5.6%, 1/18), seven patients had SD (38.9%, 7/18) and ten patients had PD (55.6%, 10/18). Thus, the response rate (RR) was 22.2% with SOX and 5.6% with sorafenib ($P = 0.154$). The disease control rate was 61.1% with SOX and 44.4% with sorafenib ($P = 0.317$).

2.3. Survival

The median progression-free survival (PFS) was 3.6 months (95% confidence interval [CI], 1.7 to 5.6) in the SOX group and 1.7 months (95% CI, 1.5 to 1.9) in the sorafenib group. PFS did not differ significantly between these two groups ($P = 0.444$, Fig. A). Median overall survival (OS) in the SOX group was 7.6 months (95% CI, 4.3 to 10.9), which did not differ significantly from the median of 4.7 months (95% CI, 2.7 to 7.3) in sorafenib group ($P = 0.246$, Fig. B). We also explored the prognostic factors for estimating the outcome in the 41 patients who remained in the follow-up. Eight potential prognostic variables were selected for univariate analysis and the subsequent multivariate analysis as required. We identified that a high ECOG PS or Child-Pugh score at baseline was associated with a significant shorter OS in multivariate analyses (Table 2). These data suggest that ECOG PS and Child-Pugh Score were two independent prognostics factors that associated with OS in patients with advanced HCC (Table 2).

2.4. Toxicity

Treatment-related toxicities were assessed after each treatment cycle. The main toxicity profiles are summarized in Table 3. No treatment-related death was observed in the either group. In the SOX group, all patients (100%, 22/22) reported side-effects at different degrees after one or two cycles, but only two patients experienced grade 3/4 toxicities (9.1%, 2/22). In the sorafenib group, the four patients lost to the follow-up were excluded from the evaluation of toxicity because the side-effects of sorafenib generally arise in accordance with the accumulated dose. In this group, 18 patients (90.0%, 18/20) had treatment-related toxicities, two of which (10.0%, 2/20) experienced grade 3/4 toxicities. SOX treatment resulted in a significantly higher prevalence of thrombocytopenia (45.5% *vs*. 5%, $P = 0.003$), elevation in transaminase levels (45.5% *vs*. 5%, $P = 0.003$) and neuropathy (36.4% *vs*. 5%, $P = 0.036$) than sorafenib. On the other hand, sorafenib treatment was associated with a significantly higher prevalence of hand–foot syndrome (60% *vs*. 0%, $P = 0.000$), diarrhea (60% *vs*. 0%, $P = 0.000$) and pruritis (40% *vs*. 0%, $P = 0.004$).

3. Discussion

Systemic cytotoxicity chemotherapy has been used for the treatment of advanced HCC for more than 30 years. However, only

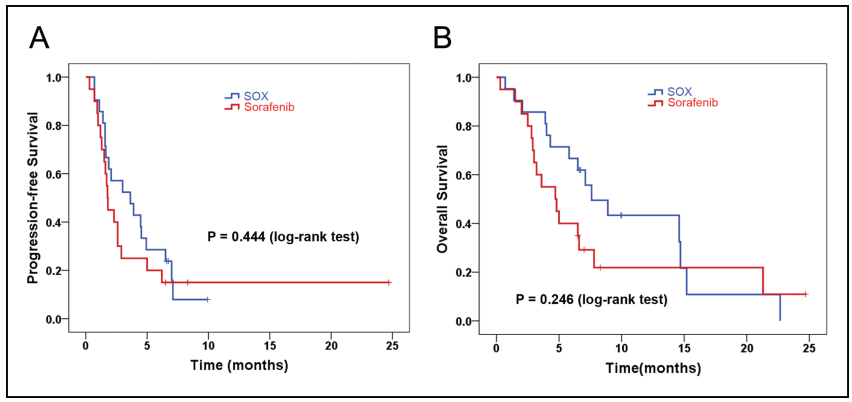

Fig. 1: Progression-free survival (A) and overall survival (B) according to treatment.

two small randomized trials were performed to compare the chemotherapy with best supportive care (BSC) (Lai et al. 1988; Ishikawa et al. 2001). Doxorubicin significantly prolonged the median survival rate compared to no antitumor therapy (10.6 weeks *vs* 7.5 weeks, $P = 0.036$), but caused fatal unpredictable complications (septicemia and cardiotoxicity) in 25% of the patients (Lai et al. 1988). Oral administration of enteric-coated tegafur/uracil improved the median survival time and one-year survival rates (12.1 *vs* 6.2 months; 55.3 *vs* 5.5%) in patients with IV-A HCC (Ishikawa et al. 2001). But the limited clinical trials are not sufficient to convincingly illustrate the benefit from the utilization of systemic cytotoxicity chemotherapy in HCC patients (Burroughs et al. 2004). On the other hand, several novel drugs or combination regimens have emerged (Asghar and Meyer 2012), however, the randomized trials comparing chemotherapy *versus* BSC are still lacking.

In contrast, sorafenib has been shown to provide a considerable survival benefit to the patients with advanced HCC in two randomized phase-III trials compared with BSC. However, the proven efficiency of sorafenib remains controversial. First of all, the effect of sorafenib should be attributed partly to the strict selection of patients, with > 95% of patients having class-A liver cirrhosis according to the Child–Pugh classification (Llovet et al. 2008; Cheng et al. 2009). Recent studies have suggested that sorafenib may be beneficial for patients with Child–Pugh class-B liver cirrhosis but it has a higher prevalence of adverse effects (Lencioni et al. 2013). Hence, the clinical utility of sorafenib for patients with Child–Pugh class-B or -C liver cirrhosis remains to be determined, and sorafenib accordingly is recommended only for the patients with Child–Pugh class-A liver cirrhosis. Second, sorafenib showed a worse outcome and less tolerability in an Asia-Pacific sorafenib trial than in the Western sorafenib trial (Cheng et al. 2009). In Asia-Pacific sorafenib trial, the median time to progression (TTP) and OS were 2.8 months and 6.5 months, whereas TTP and OS were 5.5 months and 10.7 months in the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial, respectively. The worse outcome could be ascribed to differences in the etiologic factors, clinical manifestation, and management strategy (Chen et al. 2010; Hsu et al. 2010). The disease-stabilizing effect of sorafenib generally lasts only a few months, suggesting a rapid emergence of resistance in Asian patients. Hence, developing another treatment with better efficacy is still urgently desired.

In addition, the treatment using sorafenib is restricted in some economic less developed countries. In these countries, a considerable number of HCC patients refuse using sorafenib as first-line treatment for the unbearable economic burden. Systematic cytotoxic chemotherapy was an important treatment

Table 2: Prognostics factors in univariate and multivariate analysis

Variables		n = 41	Univariate analysis			Multivariate analysis		
			mOS[a]	95% CI[b]	*P*[c]	HR[d]	95% CI	*P*
Sex	Male	37	6.5	3.7–9.3	0.750			
	Female	4	4.8	2.9–6.7				
Age(year)	≤ 45	17	4.3	2.1–6.5	0.349			
	> 45	24	7.1	5.2–9.10				
ECOG PS[e]	0	22	8.0	0.0–17.2	**0.006**	0.187	0.067-0.523	**0.001**
	1/2	19	4.0	2.4–5.6				
Child-Pugh Score	A	31	7.6	5.7–9.5	**0.001**	0.258	0.07-0.944	**0.041**
	B	10	3.2	0.0–6.5				
Extrahepatic metastasis	No	17	6.5	3.4–9.6	0.429			
	yes	24	6.5	3.4–9.5				
Underlying cirrhosis	No	16	8.9	0.0–17.8	0.074			
	Yes	25	4.7	3.2–6.2				
AFP[f] (ng/ml)	< 400	24	7.1	1.7–12.5	0.235			
	≥ 400	17	5.8	2.7–8.9				
Viral infection	Yes	11	6.6	2.2–11.0	0.434			
	No	30	6.5	3.4–9.6				
Treatment	SOX	21	7.6	4.3–10.9	0.246			
	Sorafenib	20	4.7	2.1–7.3				

a, mOS, median overall survival; **b**, 95% CI, 95% confidence interval; **c**, *P*, *P* value; **d**, HR, hazard ratio; **e**, ECOG PS, Eastern Cooperative Oncology Group Performance Status; **f**, AFP, alpha-fetoprotein

Table 3: Treatment-related toxicity (NCI-CTC[a])

Toxicity	Chemotherapy (n = 22)	Sorafenib (n = 20)	*P value*
	All grades, n (%)	All grades, n (%)	
Hematological			
Anemia	8 (36.4%)	7 (35.5%)	0.927
Leukopenia	3 (13.6%)	1 (5.0%)	0.670
Neutropenia	5 (22.7%)	2 (10.0%)	0.490
Thrombocytopenia	10 (45.5%)	1 (5.0%)	0.003
Non-hematological			
Fatigue	10 (45.5%)	9 (45.0%)	0.976
Hyperbilirubinemia	3 (13.6%)	2 (10.0%)	1.000
Transaminase elevation	10 (45.5%)	1 (5.0%)	0.003
Hand–foot syndrome	0	12 (60.0%)	0.000
Neuropathy	8 (36.4%)	1 (5.0%)	0.036
Anorexia	13 (59.1%)	11 (55.0%)	0.789
Vomiting	0	4 (20.0%)	0.093
Nausea	5 (22.7%)	8 (40.0%)	0.227
Hypertension	0	3 (15.0%)	0.199
Diarrhea	0	12 (60.0%)	0.000
Rash	0	4 (20%)	0.093
Bleeding	0	0	—
Pruritis	0	8 (40.0%)	0.004

a (NCI-CTC), Common Terminology Criteria for Adverse Events established by the National Cancer Institute

for advanced HCC in these areas and remains so. Recent retrospective studies have shown encouraging efficacy with good tolerability in HCC. Capecitabine and thalidomide gave a median OS of 9.9 months and PFS of 5.1 months in 42 patients with advanced HCC (Ang et al. 2012). In the large multicenter study involving 204 Western patients with advanced HCC treated with gemcitabine combined with oxaliplatin, the median PFS, TTP and OS was 4.5 (95% CI, 4 to 6), 8 (95% CI, 6 to11), and 11 months (95% CI, 9 to 14), respectively (Zaanan et al. 2013). The efficacy and good tolerability of the chemotherapy regimens observed in these studies raised a need to evaluate the outcome of the new regimen in compare with sorafenib.

A retrospective study comparing systemic chemotherapy with sorafenib in Korea showed that the median OS was 23.0 weeks (95% CI, 8.1 to 37.9) in the sorafenib group and 43.6 weeks (95% CI, 34.0 to 53.2) in the conventional cytotoxic therapy group. The median PFS was 11.1 weeks (95% CI, 6.5 to 15.8) *versus* 12.4 weeks (95% CI, 8.1 to 16.7) for sorafenib and conventional cytotoxic therapy, respectively. Neither parameter differed significantly (OS, $P = 0.105$; PFS, $P = 0.496$), but the data suggested that the efficacy of chemotherapy might not be inferior to that of sorafenib (Lee et al. 2012). However, the previous study was unable to set up a standard chemotherapy regimen to compare with sorafenib. Since there are no trials underway to compare sorafenib with a well-defined chemotherapy regimen directly, we performed this study to elucidate the outcome of SOX regimen in compare with sorafenib at our institution. Consistent with the finding from the retrospective study performed in Korea, the results of the present study showed the efficacy of SOX not to be inferior to that of sorafenib. Another study also reported that S-1 and platinum combination chemotherapy showed favorable efficacy, especially in the patients with lower expression of dihydropyrimidine dehydrogenase (DPD) (Kim et al. 2010).

In this study, no factor was found to significantly associate with OS in statistical analysis with the exception of ECOG PS and Child-Pugh Score. As reported previously, sex, underlying cirrhosis and the Cancer of the Liver Italian Program (CLIP) score were independent prognostic factors for OS (Qin and Tang 2002; Kudo et al. 2004; Collette et al. 2008; Tournoux-Facon et al. 2011). Our findings were not in accordance with those of other studies, which probably resulted from the small samples in our study. Extrahepatic spreading was observed more commonly before the treatment in the SOX group ($P = 0.037$), but was not associated with a significantly shorter OS in the multivariate analysis.

The treatment-related toxicity profiles were also analyzed in our study. As expected, symptomatic toxicities were more common in the sorafenib group and hematological toxicities were more common in the SOX group. Generally speaking, both of the treatments were tolerated.

The retrospective nature of our study and the limited number of involved patients not allowed us to determine the outcome of SOX regimen perfectly. Especially, the treatment options were non-randomized. For ethical considerations, it may no longer be appropriate to conduct a trial comparing chemotherapy with BSC. Sorafenib is regarded as a standard treatment for the patients with advanced HCC based on two well-designed randomized placebo-controlled trials. Thus, the outcome of SOX regimen is required to be further elucidated in a predesigned randomized trial compared with sorafenib in the future.

Despite being a retrospective investigation, this was the first study to evaluate the outcomes in terms of survival in subjects with advanced HCC treated with SOX regimen in compare with sorafenib in a single-center cohort. In conclusion, SOX regimen of chemotherapy showed promising outcome, which was presumably comparable to that of sorafenib.

4. Experimental

4.1. Patients

Data of the patients with advanced HCC treated with SOX or sorafenib were retrieved from the database of the Cancer Hospital of Guangxi Medical University (Nanning, China) from January, 2011 to March, 2013. Inclusion criteria for the retrospective analysis were: 1) diagnosis of advanced HCC proven histologically or by clinical assessment (classical arterial tumor enhancements on contrast-enhanced CT/MRI and HBV/HCV infection or serum-fetoprotein levels > 400 ng/mL); 2) not eligible for curative or local treatment; 3) ≥ 1 measurable lesion; 4) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; 5) age > 18 years, adequate function in the bone marrow and kidneys. All involved patients provided written informed consent. Our study was approved by the ethics committee of Guangxi Medical University.

4.2. Regimens

Patients in SOX group received oxaliplatin (130 mg/m^2 over 2 h) on day 1 of each 21-day cycle, in the meanwhile S-1 (40 mg/m^2) was given twice daily for 14 days, followed by a 7-day rest period. Patients in the sorafenib group were continually receiving sorafenib (400 mg) twice daily in a 28-day cycle. Patients completed at least one cycle in the either group, respectively. The treatment was continued until any of followings: 1) disease progression; 2) intolerable toxicity; 3) patient refusal; or 4) after six cycles of treatment in the SOX group.

Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Computed tomography (CT) test was repeatedly performed every two cycles during the treatment, every three months after six cycles of SOX chemotherapy, and might be earlier in patients with suspected disease progression. Treatment-related toxicity was classified by the Common Terminology Criteria for Adverse Events established by the National Cancer Institute (NCI CTC 4.0).

4.3. Statistical analyses

Progression-free survival (PFS) was defined as the time from the start of treatment to the date of disease progression or death (all causes), whichever occurred first. Surviving patients without disease progression were censored at the final follow-up date. Overall survival (OS) was defined as the time from the start of treatment until death (all causes). Surviving patients were censored at the final follow-up date. Differences in continuous and categorical variables were examined with the Student's *t*-test and χ^2 test, respectively. OS and PFS were analyzed using the Kaplan–Meier method. Differences between the curves were generated *via* a log-rank test. A Cox-regression hazard model was used for multivariate Cox proportional analyses. *P* values

were two-sided, with $P < 0.05$ indicating significance. Statistical analyses were conducted using SPSS ver16.0 (SPSS, Chicago, IL, USA).

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