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ORIGINAL ARTICLE

A phase II study of oxaliplatin in combination with doxorubicin as first-line systemic chemotherapy in patients with inoperable hepatocellular carcinoma

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Abstract
Purpose We designed a phase II trial of the combination with oxaliplatin and doxorubicin for patients with unresectable HCC to evaluate the overall response rate (ORR) and the toxicity.
Methods Forty patients with inoperable, systemic chemotherapy naive HCC were enrolled. Finally, 32 patients received oxaliplatin (130 mg/m^2) and doxorubicin (60 mg/m^2) every 3 weeks.
Results Eighty-two treatment cycles were administered (median 2 cycles, range 1–6). There was no treatment-related mortality. The ORR was 15.6% (95% CI, 3.3–28.7) with five partial responses. The median overall survival and median overall progression free survival were 31 weeks (95% CI, 22–40 weeks) and 12 weeks (95% CI, 5-19 weeks). Nausea and peripheral neuropathy were most frequent non-hematologic toxicities (nausea, $n = 15$; peripheral neuropathy, $n = 10$). The most frequent grade 3–4 hematologic adverse event was neutropenia (14 of 82 cycles) including three cases of febrile neutropenia.
Conclusions The combination of oxaliplatin and doxorubicin showed modest activity and a tolerable toxicity profile in advanced HCC patients.

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Introduction

More than 80% of patients with hepatocellular carcinoma (HCC) have cirrhosis related to chronic hepatitis B (HBV) and/or C infection [24]. Because Korea has been an area of the world to which HBV infection is endemic, HCC accounts for 12% of all malignancies and is one of the leading causes of cancer death in Korean people [3, 13]. Besides the difficulty of early diagnosis of HCC, the treatment options for inoperable HCC are often limited due to the severity of the underlying liver disease or intrahepatic dissemination of tumor. Patients with localized HCC are treated by complete surgical resection, percutaneous ablation, or liver transplantation with curative intent [4, 14]. Intra-arterial chemoembolization have shown response rates of 11–48% in several randomized trials [1, 22, 23]. However, chemoembolization is generally contraindicated for patients with extrahepatic disease or main portal vein thrombosis [14].

The palliative role of systemic chemotherapy in advanced HCC is very limited. Doxorubicin, a topoisomerase II inhibitor, is the most frequently assessed chemotherapeutic agent either as a single-agent or in combination chemotherapy regimens. Doxorubicin has shown a minimal survival advantage compared with no treatment in patient with inoperable HCC [12].

Recently, we reported a phase II study of doxorubicin and cisplatin in patients with metastatic HCC. The response rate was found to be 18.9% [95% confidence interval (CI) 8–35%] with one complete response (CR) and six partial responses (PR) out of 37 patients. However, six patients of

42 enrolled patients were dropped out due to hepatic failure and one patient expired from septic shock associated with chemotherapy [14].

Oxaliplatin, a third-generation cisplatin analogue, acts as an alkylating agent on DNA, forming platinated intrastrand cross-links between two adjacent guanine bases d(GpG) or two adjacent guanine–adenine bases d(GpA), which constitute major cytotoxic lesions. Oxaliplatin has displayed both preclinical and clinical anti-tumor activity against gastrointestinal cancers, especially colorectal cancer [19]. In early phase I trial, neither renal nor hematologic toxicities were observed. The dose-limiting toxicity was a sensory neuropathy [9]. Furthermore, oxaliplatin for patients with hepatic dysfunction was well tolerated while on a schedule of 130 mg/m^2 every 21 days [8]. Moreover, oxaliplatin does not need to hydration to prevent nephrotoxicity and, therefore, may decrease the risk of peripheral edema and ascites for patients with hepatic dysfunction. As a result, we conducted a phase II trial of combination therapy with doxorubicin and oxaliplatin in patients with inoperable metastatic HCC.

Materials and methods

Patients

Patients with histologically confirmed HCC or a combination of radiologically compatible findings to HCC, alpha-fetoprotein (AFP) >400 ng/mL and liver cirrhosis were enrolled in the study from June 2005 to May 2007. Patients were required to have inoperable HCC defined as followed: (1) patients not suitable for surgical resection, liver transplantation, or local ablation techniques in a curative intent; (2) patients with advanced disease not amenable to intra-arterial therapy because of extra-hepatic disease and/or main portal vein or hepatic vein involvement (invasion or tumor thrombus). Patients were required to be at least 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), and adequate organ function as evidenced by the following: (1) absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ per litre, (2) platelets count $\geq 100 \times 10^9$ per litre, (3) hemoglobin $\geq$10 g/dL, (4) INR $\leq$1.4, (5) total bilirubin $\leq 1.5 \times$ upper normal limit (UNL), (6) serum transaminase $\leq 5 \times$ UNL, (7) albumin $\geq$3.0 g/dL, (8) calculated creatinine clearance $\geq$50 mL/min. Patients who had received radiotherapy or chemoembolization were eligible if there was at least one measurable lesion outside the radiation field or targets of chemoembolization. Patients who had a Child-Pugh score of C, previous systemic chemotherapy, central nervous system metastases and concomitant anti-tumor therapy including tamoxifen or interferon were excluded. Patients with other malignancies, or concurrent uncontrolled medical illness were ineligible.

All patients provided written informed consent according to the institutional guideline. The clinical assessment of each patient including physical examination, chest radiograph, and clinical laboratory test includes complete blood count, serum protein, serum albumin, liver function tests, and renal function tests were performed every 3 weeks. Serum AFP was measured at the start of each cycle using an immunofluorescence assay.

Treatment schedule

The treatment cycle was begun on day 1 with intravenous oxaliplatin 130 mg/m^2 over a 2 h infusion. After oxaliplatin infusion, doxorubicin 60 mg/m^2 was administered intravenously over 30 min. The treatment was repeated every 3 weeks. Patients were treated to a maximum of six cycles unless there was documented disease progression, unacceptable adverse events or withdrawal of consent. The response to treatment was evaluated every 2 cycles by helical computed tomography (CT) according to RECIST.

Toxicity and dose modification

The toxicities were measured according to National Cancer Institute Common Toxicity Criteria version 3.0. Complete blood counts and blood chemistry were obtained before the beginning of each cycle. In cases of non-hematological grade 3–4 toxicity, doxorubicin were reintroduced at the following cycle only after recovery to grade 0–1 toxicity with a 25% dose reduction after the first occurrence, a 50% dose reduction after the second occurrence and treatment cessation after the third episode. Upon first onset of a grade 3 hematological toxicity (neutropenia or thrombocytopenia), the dose of doxorubicin and oxaliplatin were administered at 75% of the original dose and 100 mg/m^2 only after ANC and platelet counts were recovered. Patients received 75% of original dose of doxorubicin and 85 mg/m^2 of oxaliplatin after the second episode of a grade 3 hematological toxicity. Patients were dropped out upon a third occurrence of a grade 3 hematological toxicity. In the cases of grade 4 hematological toxicity, 75% of original dose of doxorubicin and 85 mg/m^2 of oxaliplatin were infused at the next treatment cycle after the first episode and the treatment was stopped if a second episode developed. When non-hematologic grade 3–4 toxicity developed, but not an allergic reaction and neuropathy, the dose of oxaliplatin was adjusted to 100 mg/m^2 after recovery to grade 1 or less. Treatment was permanently stopped in cases of any allergic reaction. If paresthesia or dysesthesias interfering with function, but

not activities of daily living, became persistent, the dose of oxaliplatin was reduced to 100 mg/m^2. When paresthesia or dysesthesias proceeded to interfere with daily activities, patients were dropped out of the protocol. Hyperbilirubinemia between 1.5 and 3.0 mg/dL required a 50% dose reduction of doxorubicin. If hyperbilirubinemia over 3.0 mg/dL was detected, treatment was ceased permanently.

Statistical analysis

The purpose of this study was to evaluate the safety and efficacy of oxaliplatin plus doxorubicin as first-line chemotherapy in patients with inoperable, metastatic HCC. The primary end point of this study was the overall response rate (ORR) and the secondary end points included the safety and tolerability, the progression free survival (PFS), overall disease control rate (ODCR) and overall survival (OS). Overall disease control rate (ODCR) represented complete response, partial response, or stable disease more than 3 weeks.

OS and PFS were estimated by the Kaplan–Meier product limit method. OS was measured from the day of beginning chemotherapy to the day of death or the last follow-up. If the patient was lost during follow-up duration, the death of patient was confirmed by telephone call to the bereaved family at the time of analysis. PFS was calculated from the day when treatment started till the date of progression, the date of death from disease, the last follow-up or the starting date of salvage chemotherapy.

The early response of serum AFP was represented by the ratio of serum AFP after first cycle to baseline AFP value. The serum AFP after first cycle meant the value of serum AFP which was followed up 3 weeks after starting of first cycle. The correlation between survival and the early response of AFP were estimated by Spearmans' rank correlation coefficient. The statistical analyses were performed using SAS Enterprise Guide 3.0 (SAS institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

This study was designed as a prospective, open-label, non-randomized single center phase II study. Sample size was calculated to reject a 10% response rate in favor of a target response rate of 30%, with a significance level of 0.05 and a power of 90% by using Simon's optimal two-stage design. In the initial stage, a total of 18 eligible patients were to be entered and evaluated for response. If there were two or less of responses, the trial was to be terminated. If three or more than three responses were observed in the first stage, then 18 additional patients were to be entered in the second stage to achieve a target sample size of 36 evaluable patients. Further assessment of the regimen was felt to be warranted if more than six responses were observed in the 36 patients.

Results

Patients' characteristics

From June 2005 to May 2007, 40 patients were recruited. However, eight patients were dropped out before starting chemotherapy, and then 32 patients received at least one cycle of both doxorubicin and oxaliplatin. Four out of eight dropped-out patients withdrew the consent and the rest could not start the chemotherapy due to worsening of organ function. The baseline characteristics of 32 patients are provided in Table 1. The median age was 50 years (range 33–67 years) and the male proportion was predominant (81%). The most common etiology for hepatitis was HBV (88%).

Table 1 Baseline characteristics of the patients

		No. of patients	% (n = 32)
Age	Median	50 years	
	Range	(33– 67)	
Sex	Male	26	81
	Female	6	19
ECOG PS[a]	0	3	9
	1	29	91
Etiology of hepatitis	Hepatitis B	28	88
	Hepatitis C	1	3
	Non-B, Non-C	3	9
Evidence of liver cirrhosis		27	78
Child-Pugh score	A	31	97
	B	1	3
Prior treatment	TACE[b]	18	56
	Surgery	12	38
	RFA[c]	5	16
	None	7	22
Extent of tumor spread	Multiple foci in liver	19	59
	Lung	16	50
	Lymph nodes	11	34
	Bone	4	13
	Portal vein thrombosis	15	47
CLIP[d] score	0	1	3
	1	10	31
	2	6	19
	3	5	16
	4	10	31
α-Fetoprotein	< 400 ng/mL	10	31
	400–10,000 ng/mL	15	47
	> 10,000 ng/mL	7	22

[a] Eastern Cooperative Oncology Group performance scale

[b] Transarterial chemoembolization

[c] Radiofrequency ablation

[d] The Cancer of the Liver Italian Program Score

Most patients had good liver function with a Child-Pugh score A (97%) and seven (22%) were newly diagnosed patients who did not receive any treatment for HCC. The most frequently involved site of extrahepatic metastases was lung (50%) and 15 patients (47%) showed evidence of portal vein thrombosis. The Cancer of the Liver Italian Program score (CLIP) of 15 patients (47%) were three or four. Including ten patients (31%) who had AFP <400 ng/mL, 13 patients had histologically confirmed HCC.

Response and survival

Eighteen patients for initial phase were enrolled up to October 2006. Four patients (22% of 18) achieved a PR, and then additional 22 patients were recruited for the second phase. Finally, 32 patients received the treatment by protocol and 28 of 32 patients were assessable for response. Five patients obtained a PR for an ORR of 15.6% (95% CI, 3.3–28.7%). ODCR including SD was 40.6% (95% CI, 24.0–58.0%). Four patients who were lost to follow-up were included in analysis of response rates (Table 2).

After a median follow-up duration of 30 weeks (range 6–101 weeks), the median OS of all 32 patients was 31 weeks (95% CI, 22–40 weeks) and the 1 year-survival rate was 29.4% (95% CI, 13.6–45.2%). The median PFS was 12 weeks (95% CI, 5–19 weeks) (Fig. 1). Ten patients were alive at the time of analysis.

Table 2 Response to treatment ($n = 32$)

Best response	No. of patients (%)
Partial response	5 (16)
Stable disease	8 (25)
Progressive disease	15 (47)
inevaluable	4 (12)
Overall response rate	5 (16%, 95% CI. 3.3–28.7%)
Overall disease control rate	13 (41%, 95% CI. 24.0–58.0%)

Three of five patients who achieved a PR had a corresponding decrease in serum AFP level as compared with the baseline value, and two patients with a PR displayed an approximate 35% decrease in serum AFP levels than the baseline value. Twenty-six patients showed higher level of AFP than normal level at baseline. Because two patients refused further follow-up evaluation and treatment after first treatment cycle, AFP data of 24 patients could be available. Of 24 patients, five (15.6%, 95% CI, 3.3–28.7%) achieved more than a 50% decrease in AFP level from baseline AFP. The early response of serum AFP showed correlation with the PFS and OS of 24 patients who had elevated serum AFP at baseline (correlation coefficient $\rho = -0.738$, $p < 0.01$ and $\rho = -0.652$, $p = 0.001$) (Fig. 2). The patients who showed 18.69 folds increase of AFP than baseline level was omitted to show because of extremely deviated value. His PFS and OS were 4 weeks and 6 weeks, respectively.

Toxicity

A total of 82 cycles were administered with median number of two cycles (range 1–6 cycles). There was no treatment-related mortality. Grade 3 or more neutropenia occurred in 14 cycles (17%) and ≥grade 3 neutropenia associated with infection occurred in three cycles (4%) of 82 cycles. Grade 3 or 4 anemia and thrombocytopenia were observed in five cycles (6%) and two cycles (2%) (Tables 3, 4).

The most frequent non-hematologic toxicity was nausea which 15 patients developed. However, there was no patient suffering from grade 3 or 4 of nausea and vomiting. Three (9%) patients of 32 patients developed grade 3 ascites and one patient could not proceed with treatment due to grade 3 abnormality of their liver function test. The CLIP scores of three patients with grade 3 ascites were three or four with portal vein thrombosis. Therefore, the investigators considered the ascites as a result of portal hypertension rather than non-hematologic toxicity of chemotherapy. One

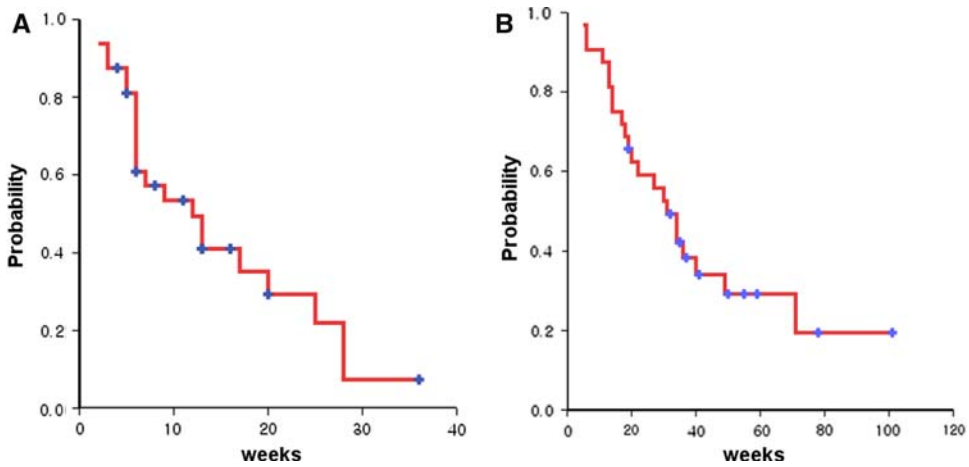

Fig. 1 Progression-free survival curve and Overall survival curve. **a** Progression-free survival curves; median progression free survival was 12 weeks (95% CI, 5–19 weeks) with 21.8% of 6-months progression free survival rate. **b** Overall survival curves; median overall survival was 31 weeks (95% CI, 22–40 weeks) with 29.4% of 1-year survival rate

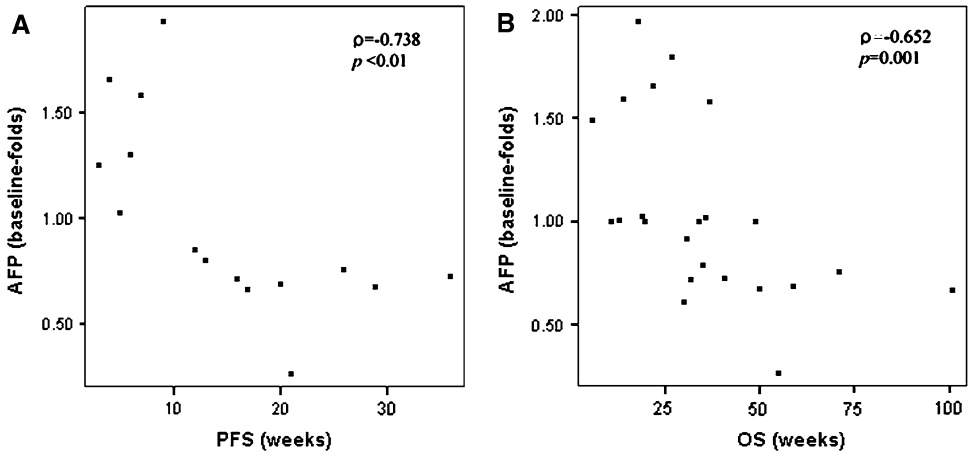

Fig. 2 The correlation between the progression-free survival and the early response of serum AFP (**a**) and the overall survival and the early response of serum AFP (**b**)

Table 3 Hematologic toxicities

	No. of cycles (n = 82)			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	5 (6%)	6 (7%)	4 (5%)	1 (1%)
Thrombocytopenia	4 (5%)	6 (7%)	1 (1%)	1 (1%)
Neutropenia	0 (0%)	4 (5%)	8 (10%)	6 (7%)
Febrile neutropenia	0 (0%)	0 (0%)	3 (4%)	0 (0%)
	9 (11%)	16 (20%)	16 (20%)	8 (10%)

There was no treatment-related mortality

Table 4 Non-hematologic toxicities

	No. of patients (n = 32)		
	Grade 1	Grade 2	Grade 3
Abnormal liver function test	2	0	1 (3%)
Nausea	8	7	0
Vomiting	4	4	0
Diarrhea	1	0	1 (3%)
Alopecia	2	3	0
Stomatitis	2	0	0
Infection without neutropenia	1	3	1 (3%)
Peripheral neuropathy	9	0	1 (3%)
Generalized weakness	3	1	0
Anorexia	4	4	1 (3%)

patient could not continue treatment due to poor performance status after an episode of neutropenic fever related to the first treatment cycle. Nine patients experienced grade 1 peripheral neuropathy and one patient suffered from grade 3 peripheral neuropathy with permanent cessation of treatment. As the protocol of dose modification, 17 interruptions and six dose reduction events in 82 cycles were occurred. The dose intensity of doxorubicin and oxaliplatin were 55 mg/m^2/3 weeks and 124 mg/m^2/3 weeks, respectively.

Discussion

The role of systemic chemotherapy in advanced HCC is known to be very limited and without demonstrable survival benefits from phase III trial [20]. Doxorubicin, a topoisomerase II inhibitor, has been considered one of the most active agents in advanced HCC. Based on favorable results from early phase II trials, several randomized phase III trials were conducted to compare the efficacy of doxorubicin with 5-fluorouracil-based chemotherapy and etoposide [6, 11, 18, 21, 28]. However, those trials failed to show survival benefit, even if higher response rates were achieved [6, 18]. Recent phase II studies and retrospective analyses have not achieved response rates over 20% [5, 7, 10, 26]. In a systemic review of clinical trials, six of ten randomized controlled trials tested doxorubicin versus non-doxorubicin-containing regimens and revealed that the 1-year survival rate was higher for the doxorubicin-containing regimen [27]. A phase II study of doxorubicin and cisplatin conducted at our center showed an 18.9% ORR (95% CI, 8.0–35%) and a 7.3 month median OS. The most common grade 3–4 toxicities were neutropenia (14.3%), thrombocytopenia (11.9%), and diarrhea (9.5%). However, six of 42 enrolled patients had to stop the treatment due to hepatic dysfunction [14]. The combination of doxorubicin and oxaliplatin, in the current study, showed the tolerable toxicity profiles, especially in terms of hepatic dysfunction. One patient could not receive further treatment because of grade 3 liver function abnormality. Although three patients developed grade 3 ascites, 3 or 4 CLIP score and the presence of portal vein thrombosis were supported that ascites resulted from decompensate cirrhosis rather than toxicity of chemotherapy. Therefore, the combination of oxaliplatin and doxorubicin seemed to be more beneficial to advanced HCC patients than cisplatin and doxorubicin considering of slightly lower ORR and more tolerable toxicities.

Because of the impairment of hepatic function associated with liver cirrhosis, the options for systemic chemotherapy

for patients with HCC are limited. Oxaliplatin, a third-generation cisplatin analogue, recently demonstrated tolerable hepatic toxicity to the patients with hepatic dysfunction. Oxaliplatin with a schedule of 130 mg/m^2 every 21 days was well tolerated [8]. Moreover, there were two phase II studies of oxaliplatin-based combination chemotherapy for patients with advanced HCC [4, 16]. Boige et al. reported an ORR of 6% with oxaliplatin and capecitabine. Most common grade 3–4 toxicities were abnormal liver function test (16%), diarrhea (12%), and thrombocytopenia (12%) [4]. A phase II study of gemcitabine and oxaliplatin demonstrated an 18% ORR with 11.5 month median OS and 6.3 months median PFS. Gemcitabine and oxaliplatin regimen also showed good tolerability with a 27% occurrence of grade 3–4 thrombocytopenia and 24% of grade 3–4 neutropenia [16].

Emerging development of molecular targeted therapies, bevacizumab, a recombinant, humanized monoclonal antibody targeting vascular endothelial growth factor receptor, showed relatively promising efficacy as monotherapy for advanced HCC. Schwartz et al. and Malka et al. reported preliminary results of phase I and phase II study on bevacizumab [17, 25]. Schwartz et al. [25] demonstrated that 11 of 13 patients who were treated with bevacizumab alone achieved disease control more than 4 months. Another phase II study of bevacizumab monotherapy for advanced HCC patients showed 67.5% of disease control rate including 12.5% of partial response [17]. Moreover, a recent phase II study of bevacizumab plus gemcitabine and oxaliplatin demonstrated an ORR of 18% with median OS was 9.6 months and median PFS was 5.3 months [30]. On other hand, sorafenib, an oral multikinase inhibitor that targets Raf kinase and receptor tyrosine kinases, demonstrated modest efficacy as a single agent. Although 2.2% of PR, single-agent sorafenib demonstrated 4.2 months of median PFS and a 9.2 month median OS. In addition, relatively tolerable toxicity profiles were observed with the most common grade 3–4 toxicities to include fatigue (9.5%), diarrhea (8.0%), and hand-foot skin reaction (5.1%) [2]. Recently the US Food and Drug Administration (FDA) approved sorafenib for patients with inoperable liver cancer based on the results of a randomized placebo-controlled trail. A phase III randomized trial of sorafenib for inoperable HCC patients showed the longer survival of sorafenib group compared with placebo group (Hazard ratio 0.69, $p = 0.00058$). The median OS and the median time to progression of sorafenib group were 46.3 weeks and 24.0 weeks. Even though seven of 299 patients achieved PR, the progression-free rates at 4 months were 62% with 73% prolongation in time to progression [15].

In the current study, the combination chemotherapy with doxorubicin and oxaliplatin demonstrated a 16% ORR. This was not inferior to the result of a previously reported randomized phase III trial with cisplatin, interferon α-2b, doxorubicin and fluorouracil (PIAF). PIAF showed 20.9% (95% CI, 12.5–29.2%) ORR compared to 10.5% with single agent doxorubicin. The tolerability of doxorubicin and oxaliplatin compared to PIAF was notable for a decreased frequency of neutropenia (22 vs. 82%) and thrombocytopenia (14 vs. 57%) [29]. Although three patients (9%) developed intractable ascites in the current study, it was relatively tolerable after consideration of high CLIP score and portal vein thrombosis. Furthermore, our study showed the possibility of following serum AFP as a predictive marker under treatment on PFS and OS. In univariate analysis, PFS and OS did not correlate with the value of serum AFP at baseline, but the early decrease of serum AFP.

In conclusion, the doxorubicin and oxaliplatin regimen showed tolerable toxicity profiles and the modest antitumor activity compared with previously reported cytotoxic chemotherapeutic regimens. However, the approval of sorafenib for inoperable HCC patients changed the systemic therapeutic strategies of HCC. Nevertheless, sorafenib showed survival benefit compared with placebo, the major antitumor activity of sorafenib is the inhibition of tumor growth and the search for the optimal systemic chemotherapy continues. In order to improve the efficacy of systemic therapy for patients with advanced HCC, therefore, the doxorubicin and oxaliplatin regimen may be still worth considering as a systemic chemotherapy option combined with molecular targeted therapies such as sorafenib or as the salvage chemotherapy after sorafenib treatment, because of its modest antitumor activity and favorable tolerability.

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