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ORIGINAL ARTICLE

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Phase II study of doxorubicin and cisplatin in patients with metastatic hepatocellular carcinoma

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Abstract *Objective*: The outcome of systemic chemotherapy in metastatic hepatocellular carcinoma (HCC) patients had been disappointing. Based on the demonstrated antitumor activities and different mechanisms of action and toxicity profiles, we designed a phase II trial of combination therapy with doxorubicin and cisplatin in metastatic HCC patients anticipating a synergistic interaction of the combination. *Methods*: From January 1998 to January 2003, 42 consecutive patients with metastatic HCC were accrued. The regimen consisted of doxorubicin 60 mg/m^2 delivered as an intravenous infusion over 30 min on day 1, followed by cisplatin 60 mg/m^2 infused over 1 h on day 1. The cycle was repeated every 28 days. The objective tumor response was evaluated after two or three courses of chemotherapy. The serum alpha-fetoprotein level was measured at the start of every cycle. *Results*: In total, 122 cycles of the regimen were administered, with a median of three cycles per patient (range one to eight cycles). The median age of the patients was 45 years (range 19–61 years), and 37 were evaluable for treatment response. The objective response rate was 18.9% (95% CI 8.0–35%) with one complete response and six partial responses. Six patients (16.2%) had stable disease and 24 patients (64.9%) had progression. Median overall survival of 37 patients was 7.3 months (95% CI 5.9–8.6 months). The median time to progression of all evaluable patients was 6.6 months (95% CI 5.4–7.8 months). Of 37 evaluable patients, 12 32.4%, 95% CI 18.0–49.8%) showed more than 50% decrease in AFP level from their baseline AFP and the median time to decrease in AFP by more than 50% was 1.8 months with a range of 0.7–4.7 months. The chemotherapy was well tolerated and the most common grade 3/4 side effects were neutropenia (14.3%), thrombocytopenia (11.9%), and diarrhea (9.5%). *Conclusion*: Combination chemotherapy with doxorubicin and cisplatin in metastatic HCC patients showed modest antitumor activity with relatively tolerable adverse effects. The objective response rate of the regimen was comparable to those found in other phase II trials, but the search for the optimal chemotherapy should be continued.

Keywords Doxorubicin · Cisplatin · Hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, especially in Asia. In Korea, HCC accounts for 12% of all malignancies and is one of the leading causes of cancer death [2]. Although the only potential curative treatment modality is complete surgical resection, the overall operability rate for HCC is between 9% and 27% [10, 18]. Most patients present with inoperable HCC and the treatment options

are often limited for these patients due to the severity of the underlying liver disease or intrahepatic dissemination of tumor. Patients with inoperable but localized HCC may achieve long-term complete response to transarterial chemoembolization, percutaneous ablation, or liver transplantation. Therapeutic options are further narrowed in the presence of extrahepatic disease or main portal vein thrombosis where locoregional therapy or chemoembolization is generally contraindicated.

The role of systemic chemotherapy in advanced HCC is known to be very limited although various single-agent or combination therapies have been tested. Doxorubicin, a topoisomerase II inhibitor, is the most commonly used drug either in single-agent or combination chemotherapy regimens for HCC and has shown a response rate of 20% with a median survival of 4 months in 13 trials [22]. Patients with inoperable HCC who receive doxorubicin show a minimal survival advantage when compared with no treatment [9]. Cisplatin has shown an objective response rate of 17% as single-agent chemotherapy [7] and a higher response rate (26–47%) when combined with epirubicin, 5-fluorouracil (5-FU) or doxorubicin, interferon alpha and 5-FU [6, 17, 19, 20]. Based on the demonstrated antitumor activities and different mechanisms of action and toxicity profiles, we designed a phase II trial of combination therapy with doxorubicin and cisplatin in metastatic HCC patients anticipating a synergistic interaction of the combination.

The aim of this study was to evaluate the objective response and assess the efficacy and toxicities of the combination regimen of doxorubicin and cisplatin in metastatic HCC patients.

Patients and methods

Patient selection

Patients with histologically confirmed and radiologically measurable HCC were enrolled in the study from January 1998 to January 2003. Patients were eligible for entry if they had portal vein thrombosis, metastatic HCC and with Okuda stage I/II disease. Patients were not allowed to receive any other forms of therapy, such as radiation, transcatheter arterial chemoembolization (TACE) within 4 weeks prior to enrollment. Patients were required to be at least 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and have estimated life expectancy of at least 3 months. Required laboratory data included adequate bone marrow function (absolute neutrophil count $>1500\ \mu l^{-1}$, platelet count $>100{,}000\ \mu l^{-1}$, hemoglobin ≥10 g/dl), normal renal and hepatic functions (serum creatinine <1.5 mg/dl, creatine clearance >60 ml/min, total bilirubin <3.0 mg/dl, serum transaminase less than 2.5 times the normal level). Patients who had received radiotherapy were eligible if there was at least one measurable lesion outside the radiation field. Serum alpha-fetoprotein (AFP) was measured at the start of each cycle using an immunofluorescence assay.

All patients provided written informed consent before any study-specific procedures were performed. The clinical assessment of each patient including physical examination, chest radiograph, and clinical laboratory tests (hematology and blood chemistry) were performed at all visits. Tumor assessments were performed every two or three treatment cycles. Adverse events were monitored throughout the study.

Treatments

Chemotherapy was given on an outpatient basis. The regimen consisted of doxorubicin 60 mg/m^2 delivered as an intravenous infusion over 30 min on day 1, followed by cisplatin 60 mg/m^2 infused over 1 h on day 1. The cycle was repeated every 28 days provided there was no evidence of progressive disease or treatment-related toxic effects, for up to six cycles of chemotherapy.

Toxicity and tumor response criteria

Toxicity was assessed for each cycle and graded according to WHO toxicity criteria [16]. Complete blood counts and blood chemistry were obtained before the beginning of each cycle. The protocol allowed the dose of doxorubicin to be reduced by 25% if there was grade 4 hematologic toxicity. A dose reduction of 25% of doxorubicin was allowed when transaminases were elevated more than 2.5 times the baseline values within 3 weeks from administration of doxorubicin. The protocol was stopped if either grade 4 toxicity or clinical deterioration considered not amenable to further treatment was present.

A complete response was defined as disappearance of all clinically detectable disease for at least 4 weeks. Partial response was defined as a ≥50% decrease in tumor size without the appearance of new disease or increase in any single lesion of more than 25%. Stable disease was defined as no significant change in measurable or assessable malignant disease without the appearance of new lesions. This included a less than 50% decrease in tumor size and a less than 25% increase in any tumor site. Stable disease required no worsening in performance status. Progressive disease was defined as a decline in performance status, the appearance of new malignant lesions, a ≥25% increase in measurable disease (≥25% increase in estimated size for assessable disease) at any site of more than 2 cm^2, or a ≥50% increase in size for any site of less than 2 cm^2 in size at the initiation of treatment.

Statistical analysis

The primary end-point was the response rate, and the secondary measures were survival and time to progres-

sion. Time to progression of disease was calculated from the first cycle of chemotherapy. Survival was defined as the time elapsed from the starting date of chemotherapy to the date of death or the last follow-up. Survival rates and time to progression were assessed by the Kaplan–Meier method.

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 [21]. In the initial stage, a total of 18 evaluable patients were to be entered and evaluated for response. If there were fewer than two responses, accrual was to be terminated. If 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

Patient characteristics

From January 1998 to January 2003, 42 consecutive patients with metastatic HCC were accrued. The clinical characteristics of the enrolled patients are shown in Table 1. The median age of the patients was 45 years, ranging from 19 to 61 years. All 42 patients (36 men and 6 women) received at least one cycle of doxorubicin and cisplatin, and 37 patients were evaluable for treatment response. Zubrod performance status scores were 0 in six patients (14.3%), 1 in 26 patients (69.0%), and 2 in 7 patients (16.7%). A majority of the patients (85.7%) had liver cirrhosis and 35.7% of patients had prior liver resections (lobectomy, segmentectomy). Most patients had Child-Pugh class A (88.1%), and most (83.3%) had abnormal serum AFP level (> 9.6 ng/ml), with a median value of 2355 ng/ml (range 1.0–125,000 ng/ml). Regarding tumor status, 54.8% of patients had pulmonary metastases, 52.4% had main portal vein thromboses, and 16.7% had both lung metastases and portal vein thromboses. The Cancer Liver Italian Program (CLIP) scores [24] were 0 ($n = 10$), 1 ($n = 12$), 2 ($n = 5$), 3 ($n = 8$), and 4 ($n = 7$).

Table 1 Patient characteristics

Total no. of patients	42
Age (years)	
Median	45
Range	19–61
Sex, *n*	
Male	36
Female	6
Performance status 0/1/2, *n*	6/29/7
Okuda stage I/II, *n*	18/24
Child classification A/B/C, *n*	37/5/0
Hepatitis virus status, *n* (%)	
HBsAg(+)	36 (85.7)
Anti-HCV(+)	2 (47.6)
None	4 (9.5)
Previous treatment, *n* (%)	
Surgery	15 (35.7)
Transcatheter arterial chemoembolization	9 (21.4)
α-Fetoprotein, *n* (%)	
< 400 ng/ml	18 (42.9)
400–10,000 ng/ml	9 (21.4)
> 10,000 ng/ml	15 (35.7)
Liver cirrhosis, *n* (%)	36 (85.7)
Pretreatment laboratory data, median (range)	
Bilirubin (mg/dl)	0.75 (0.1–2.9)
Albumin (g/dl)	3.75 (2.2–4.4)
Aspartate transaminase (U/l)	81.0 (16.0–188.0)
Alanine transaminase (U/l)	49.0 (11–161)
Platelet count ($\times 10^3$/ml)	177.5 (10.0–582.0)
Tumor status, *n* (%)	
Main portal vein thrombosis	22 (52.4)
Extrahepatic metastasis	
Lung	23 (54.8)
Lymph node	4 (9.5)
Bone	2 (4.8)
Brain	1 (2.4)
Intrahepatic metastasis, *n* (%)[a]	6 (14.3)

[a]Patients with intrahepatic metastasis were not candidates for local therapy such as resection, radiofrequency ablation, or ethanol injections due to simultaneous metastasis to other sites.

Table 2 Treatment results

Response	No. of patients (%)
Complete response	1 (2.7)
Partial response	6 (16.2)
Stable disease	6 (16.2)
Progressive disease	24 (64.5)
AFP response (> 50% decrease)	12 (32.4)

Tumor response and survival

In total, 122 cycles of the regimen were administered, with a median of three cycles per patient (range one to eight cycles). Antitumor response could be radiologically assessed in 37 of 42 patients, as shown in Table 2. Five patients were lost to follow-up, and the treatment response could not be determined. The objective response rate was 18.9% (95% CI 8.0–35%) with one complete response and six partial responses. Six patients (16.2%) had stable disease and 24 patients (64.9%) had progression. One patient with a complete response initially presented with an 8-cm mass in the left lobe of the liver with direct invasion of the diaphragm and pericardium and received en bloc resection of the diaphragm and pericardium in addition to liver tumorectomy. He developed multiple hematogenous lung metastases 2 months later. After six cycles of chemotherapy, a complete radiologic complete response was attained and there had been no evidence of recurrence for 5 months to the time of this report. Five patients who had a partial response later experienced disease progression; the median time from their response date to progression was 9.1 months (range 7.3–23.9 months). Median overall

survival of 37 patients was 7.3 months (95% CI 5.9–8.6 months). The estimated 1-year survival was only 20% (Fig. 1). The median time to progression of all evaluable patients was 6.6 months (95% CI 5.4–7.8 months).

Five of seven patients who achieved a partial response had a corresponding decrease in serum AFP level as compared with the baseline value (median decrease of 86.9%), and two patients with a partial response did not have elevated serum AFP levels at baseline. Of 37 patients, 12 (32.4%, 95% CI 18.0–49.8%) showed more than 50% decrease in AFP level from their baseline AFP and the median time to decrease in AFP by more than 50% was 1.8 months with a range of 0.7–4.7 months (Table 2). The median survival time in patients who showed a reduction in AFP level by 50% was 7.6 months (95% CI 5.1–10.2 months), while that in other patients was 6.4 months (95% CI 3.6–9.3 months, $P = 0.9$). In a univariate analysis, a serum bilirubin less than 0.5 mg/dl predicted a good response to treatment ($P = 0.049$).

Toxicity

All patients were evaluable for toxicity (Table 3). The most common grade 3/4 toxicities were neutropenia (14.3%), thrombocytopenia (11.9%), and diarrhea (9.5%). Of two patients with grade 4 granulocytopenia, one patient experienced a transient febrile episode with spontaneous recovery and one patient died from sepsis. Three patients (7.1%) refused further chemotherapy after one cycle due to prolonged nausea and/or anorexia. Six patients (14.3%) stopped chemotherapy after one cycle because of a deterioration of liver function. The cause of hepatic failure, either from chemotherapy or disease progression, could not be clinically confirmed.

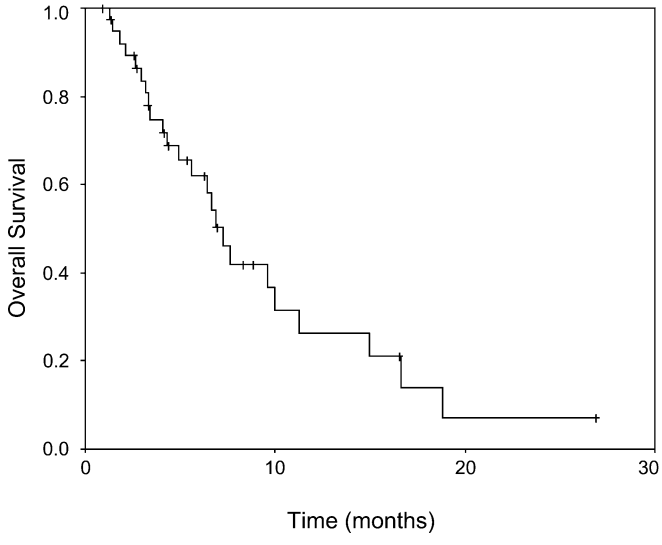

Fig. 1 Overall survival of metastatic HCC patients treated with doxorubicin and cisplatin

Table 3 Toxicity profile

	Grade 3, *n* (%)	Grade 4, *n* (%)
Hematologic		
Anemia	2 (4.8)	–
Leukopenia	4 (9.5)	2 (4.8)
Thrombocytopenia	5 (11.9)	–
Non-hematologic		
Hyperbilirubinemia	3 (7.1)	–
Nausea/vomiting	3 (7.1)	–
Diarrhea	3 (7.1)	1 (2.4)
Skin rash	–	–
Stomatitis	1 (2.4)	–
Alopecia	4 (9.5)	–
Anorexia	4 (9.5)	1 (2.4)
Fatigue	5 (11.9)	–
Morbidity and mortality		
Hepatic failure	6 (16.2)	
Treatment-related death[a]	1 (2.7)	

[a]The cause of death was septic shock.

Non-hematologic toxicities included nausea, vomiting, alopecia, and fatigue, which were usually grade 1 or 2. No patients experienced renal failure from cisplatin or cardiac toxicity from doxorubicin.

Discussion

HCC has been considered to be a chemotherapy-resistant tumor and currently there is no standard chemotherapy for metastatic HCC patients. There are no prospective randomized trials suggesting that systemic chemotherapy prolongs survival when compared with no treatment. Furthermore, there is no conclusive evidence that combination chemotherapy is superior to single-agent chemotherapy in advanced HCC. Single chemotherapeutic agents, which have demonstrated a consistent response rate of more than 10% are 5-FU, doxorubicin, and cisplatin [5, 8, 9, 14]. Most phase II studies of doxorubicin-based chemotherapy have shown an objective response rate from 13% to 26% [1, 3, 12, 21]. In a systemic review of clinical trials [23], six of ten randomized controlled trials tested doxorubicin vs non-doxorubicin-containing regimens and found that the 1-year survival rate was higher for the doxorubicin-containing regimen. Recently, Leung et al. have conducted a phase II study using a PIAF regimen (cisplatin, doxorubicin, 5-FU, and interferon-α2b) in 50 unresectable HCC patients and reported a 26% partial response rate with a median survival of 8.9 months [12]. The notable finding of the study was that nine patients with partial response were able to receive surgical resection resulting in complete pathologic remission in four patients. This study indicates the strong possibility that aggressive systemic combination chemotherapy may result in complete pathologic remission. However, the regimen was associated with considerable toxicities with significant myelosuppression (34%), which resulted in two deaths from sepsis. A few small phase II studies in

advanced HCC using newer agents such as paclitaxel, capecitabine, and gemcitabine have shown minimal antitumor activities ranging from 0% to 17.8% [4, 16, 25].

In an attempt to achieve better results with doxorubicin, we combined doxorubicin with cisplatin seeking a synergistic effect in metastatic HCC patients who had no therapeutic alternatives. These two drugs lack overlapping toxicity profiles and mechanisms of action. In this clinical trial, the objective response rate was 18.9% and the median overall survival was 7.3 months. The 1-year survival rate was only 20% in our series. Llovet et al. have reported a 1-year survival of 54 untreated HCC patients with poor performance, constitutional symptoms, vascular invasion, or extrahepatic spread of 29% with a median survival of 5.4 months [15]. Although it would be difficult to directly compare these data with the results of our study, a survival benefit from doxorubicin and cisplatin therapy in metastatic HCC seems unlikely, despite the acceptable response rate shown in our series. The median time from the response date to progression in partial responders who later had progression was 9.1 months. There are no reported clinical trials in which the efficacy of combination therapy with doxorubicin and cisplatin has been assessed, except for one small study from Korea, which demonstrated a response rate of 36% (5/14) [11]. However, due to the small cohort of patients in this study ($n = 14$), there is a difficulty in comparing their study with our series. The response rate of our regimen is comparable to those found in most phase II studies of doxorubicin-based combination therapy ranging from 13% to 26% [1, 3, 5, 8, 9, 14].

The median time to decrease of serum AFP by 50% from the baseline value was 1.8 months and 32.4% of assessable patients showed a significant reduction in serum AFP ($< 50\%$) in this study. Leung et al. have suggested that conventional radiologic assessment of response might not necessarily reflect the true extent of tumor cell kill [12]. The median survival time in patients who showed a reduction in AFP level by 50% was 7.6 months (95% CI 5.1–10.2 months), while that in other patients was 6.4 months (95% CI 3.6–9.3 months, $P = 0.9$).

Because of a low response rate and poor hepatic functions in advanced HCC patients, a search for predictive factors for treatment response in these patients is necessary. In a multivariate analysis of 149 patients with inoperable HCC, Leung et al. have shown that a lower serum bilirubin level and the absence of cirrhosis are correlated with treatment response and prolonged survival [13]. A serum bilirubin level less than 0.5 mg/dl was correlated with a good response in univariate analysis. The predictive factors for favorable treatment response reflect the underlying liver function, which is a major determinant of prognosis in HCC. It has been suggested that any tumor-killing effect by a chemotherapeutic drug may be underestimated when the conventional response criteria are used, because a patient's survival is mainly determined by the underlying liver function.

The studied regimen was relatively well tolerated despite the fact that a majority of patients had liver cirrhosis. Most grade 3/4 hematologic toxicities spontaneously recovered in 1 or 2 weeks. Of two patients with grade 4 febrile neutropenia, one died of neutropenic septic shock. The major concern of the regimen was its hepatic toxicity. Six patients stopped further chemotherapy after one cycle because of deterioration of hepatic function of which the cause was not definite. The dose of doxorubicin was also reduced by 25% due to elevated hepatic enzyme levels after chemotherapy in 13 cycles (10.7%).

In conclusion, the combination chemotherapy with doxorubicin and cisplatin in metastatic HCC patients showed modest antitumor activity with relatively tolerable adverse effects, although the hepatotoxicity of doxorubicin remains a concern. The objective response rate of the regimen was comparable to those found in other phase II trials. However, the search for the optimal systemic chemotherapy in metastatic HCC patients should be continued and clinical trials on new novel antitumor agents are still warranted.

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