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ORIGINAL ARTICLE

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Phase II study with a combination of epirubicin, cisplatin, UFT, and leucovorin in advanced hepatocellular carcinoma

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Abstract *Purpose*: Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Because HCC usually presents as an advanced disease and occurs in the background of liver cirrhosis, most patients are not suitable for treatment with curative intent, thus effective systemic chemotherapy is required. However, the outcome of systemic chemotherapy has been disappointing in advanced HCC. This study was conducted to test the efficacy and toxicity of the combined regimen of epirubicin, cisplatin, and UFT moderated by leucovorin in advanced or recurrent HCC. *Patients and methods*: All 53 patients received epirubicin (50 mg/m^2 i.v.) on day 1 and cisplatin (60 mg/m^2 i.v.) after epirubicin administration. Oral UFT 400–600 mg/day, determined by body surface area, and leucovorin 75 mg/day were administered for 21 consecutive days, followed by a 7-day drug free interval. *Results*: Nine had a partial response, representing 16.9% of response rate (95% confidence interval rate; 7.0–26.8%) with median response duration of 17.1 weeks (95% CI; 5.0–29.3 weeks, range; 7.1–51.7 weeks). Fifteen patients had stable disease and the disease progressed in 26 patients. The median overall survival for the patients was 24.6 weeks (95% CI; 17.3–31.9 weeks, range; 3.0–131.3 weeks). The main toxicities were hematologic toxicities including neutropenia, which reached grade 3/4 in 17 patients (38.5%), and grade 3 or 4 thrombocytopenia in five patients (9.4%). *Conclusion*: The combination of epirubicin, cisplatin, and UFT moderated by leucovorin showed modest anti-tumor activity with relatively tolerable toxicities. However, a randomized phase III trial based on this regimen is warranted to clarify its survival benefit in patients with advanced HCC.

Keywords Hepatocellular carcinoma · Chemotherapy · Epirubicin · Cisplatin · UFT

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer mortality worldwide. Especially, HCC is one of the leading causes of cancer-related death in the Asia-Pacific region including Korea. High prevalence of chronic hepatitis B (HBV) and HBV-associated liver cirrhosis account for this HCC mortality rates in the Asia-Pacific region [1]. Although complete surgical resection is the only curative treatment modality, most patients are not suitable for surgical resection because of the extent of disease or underlying liver disease, or both. Thus, the overall operability rate for HCC is only 10–20% at diagnosis and its 5-year disease-free survival is less than 20% [2–4]. With regard to treatments against the advanced stage of the disease, various treatment modalities have been trialed including cryotherapy, radiotherapy, systemic and intra-arterial chemotherapy and so forth. For patients with inoperable but localized disease, arterial chemoembolisation has been preferred and a meta-analysis of seven randomized controlled trials showed its benefit over palliative treatment alone [5]. However, the severity of underlying liver disease or the presence of extrahepatic disease limited this locoregional treatment, thus, not all patients are suitable for chemoembolisation.

Systemic chemotherapy in advanced HCC has been regarded as ineffective because of its lack of responsiveness or high rate of toxicities, although various single-agent or combination chemotherapies have been investigated in the past 30 years [6–10]. Considering the large number of patients with advanced disease not suitable for locoregional treatments, the development of effective systemic chemotherapy is essential to improve the prognosis for patients with this disease.

Doxorubicin has been widely investigated either in single-agent or combination therapy for patients with advanced HCC since the first phase II study that showed 79% response rate with 75 mg/m^2 doxorubicin in Ugandan patients [11]. However, subsequent trials with single-agent doxorubicin have failed to show response rates over 20% [12–14]. A randomized trial compared doxorubicin with supportive care alone showed a significant survival benefit: 10.6 weeks of median survival in doxorubicin group versus 7.5 weeks in supportive care group ($P = 0.036$) [15]. However, they concluded doxorubicin was not an ideal drug for inoperable HCC because of high treatment-related death rate (25%). More recent trials of doxorubicin in combination have not shown superior response rates or survival benefits over doxorubicin alone [16, 17]. Epirubicin, another anthracycline known to have less severe cardiotoxicity than doxorubicin, has shown tolerable toxicity profiles but failed to show response rates superior to doxorubicin in phase II trials [18, 19]. However, higher response rates have been reported using epirubicin and etoposide together suggesting the efficacy of epirubicin in combination, although considerable hematological toxicity was observed [20]. Thus, a newer epirubicin combination regimen is warranted to reduce toxicity keeping its efficacy.

5-fluorouracil (5-FU), fluoropyrimidine analog is considered as an active agent against various gastrointestinal malignancies, thus widely used in advanced HCC [21–23]. Considering the schedule-dependency of fluoropyrimidine, increased efficacy can be expected when given as a continuous infusion. However, continuous infusion is cumbersome for patients because it needs permanent intravenous access. Therefore, oral 5-FU or prodrug (tegafur) can be used more comfortably in patients if they can achieve plasma levels similar to continuous infusion. UFT is an oral prodrug form of 5-FU that combines uracil and tegafur in a 4:1 ratio and tegafur is converted to 5-FU by in vivo metabolism. Uracil can also inhibit dihydropyrimidine dehydrogenase (DPD), an enzyme that degrades 5-FU. Thus, UFT can increase the bioavailability of oral 5-FU and long-term oral administration of UFT was reported to be as effective as intravenous 5-FU [24, 25].

Based on these results, we designed a newer combination regimen combining epirubicin and oral UFT instead of 5-FU intravenous infusion, and leucovorin to moderate the anti-tumor effect of UFT. In addition to this combination, we added cisplatin, which has shown a higher response when combined with epirubicin and 5-FU in hepatobiliary tumors [26]. In this study, we determined the efficacy and toxicity of combination chemotherapy with epirubicin, cisplatin, and oral UFT moderated by leucovorin in patients with advanced HCC.

Materials and methods

Patient eligibility

Patients with histologically confirmed and radiologically measurable HCC were included in this study between September 2000 and August 2004 at Korea University Medical Center (KUMC). Patients had HCC, which was initially inoperable, or recurrent or progressing after local treatment such as surgery or transarterial chemoembolisation. Patients were not allowed to get any other local therapeutic modalities within 4 weeks prior to enrollment. Other eligibility criteria were performance status of ≤ 2 on ECOG (Eastern Cooperative Oncology Group) scale, life expectancy of ≥ 2 months, serum creatinine ≤ 2 mg/dl, serum total bilirubin ≤ 3.0 mg/dl, adequate bone marrow function with absolute neutrophil count $\geq 1{,}500/\ \mu$l and platelet count $\geq 60{,}000/\ \mu$L, and at least one measurable lesion. Contraindications to entry included an active infectious process, active heart disease, central nervous system involvement, or any concomitant second primary cancer. We have got written informed consents from all patients enrolled into this study. The institutional review board of KUMC approved the study protocol.

Treatment plan

The epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) were administered intravenously on the first day of each cycle at the hospital. Intravenous hydration for 2 h was done before cisplatin infusion to prevent nephrotoxicity. UFT and leucovorin were orally administered for 21 consecutive days from day 1, and were followed by a 7 day treatment free interval. The total daily UFT dose (determined by tegafur dosage) was determined at three levels according to body surface area (> 1.75 m^2:600 mg/day, between 1.75 m^2 and 1.25 m^2:500 mg/day, < 1.25 m^2:400 mg/day) and it was divided into three doses. UFT was supplied as a capsule, which contained 100 mg of tegafur plus 225 mg of uracil. A total of 75 mg of oral leucovorin was divided into three doses without consideration of body surface area. This schedule was repeated every 4 weeks until tumor progression or until the development of treatment intolerance. Dolasetron 100 mg was administered before epirubicin infusion and lorazepam 0.5 mg was administered twice a day to prevent delayed emesis and oral metoclopropamide was prescribed during UFT and

leucovorin administration. Patient compliance for UFT was verified by counting of remaining pills or an interview at the end of each treatment course.

Toxicity evaluation and dosage modification

Toxicity was evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0. For the case of grade 3 or more hematologic toxicity, epirubicin and cisplatin were initiated at a reduced dose by 25%. In case of grade 4 neutropenia, granulocyte colony-stimulating factor was administered intravenously until hematological toxicity was recovered. For grade 3 or 4 gastrointestinal toxicity, the dosage of UFT was reduced by one level (i.e., decremented by 100 mg/day). UFT and leucovorin were held in the case of severe non-hematologic toxicity, and restarted after symptoms resolved. Treatment was postponed by 1 week until the toxicity resolved, when severe toxicity was noticed at the time of scheduled treatment. If drug administration was delayed for more than 2 weeks, the study was terminated.

Response evaluation

Treatment response was assessed by computed tomography (CT) every two cycles of treatment. Thus, when the objective response was observed, it was monitored by subsequent CT scans. If disease progression was suspected including clinical deterioration or elevation of alpha-fetoprotein, response evaluation was done earlier than planned such as after the first course of treatment. For the evaluation of response, the World Health Organization (WHO) criteria were adopted [27]. Complete response (CR) was defined as disappearance of all previously measurable lesions and absence of any new tumor lesions. Partial response (PR) was defined as a decrease of at least 50% in the product of two perpendicular diameters of each measurable lesion. Stable disease (SD) was defined as decrease of $<50\%$ or an increase of $<25\%$ in tumor size and progressive disease (PD) was defined as a $>25\%$ increase in the tumor products of the two diameters of at least one tumor, or as the presence of a newly developed lesion. Tumor response was assessed by the department of diagnostic radiology in our hospital. Three radiologists who majored in gastrointestinal radiology reviewed the results of imaging studies, mainly CT images. If there are differences between their opinions, they made a decision by consensus conference.

Statistics

All enrolled patients were included in the intention-to-treat analysis of efficacy. The trial was conducted using response rate as the primary end-point. Sample size was calculated to reject a 10% response rate in favor of a target response rate of 30%. Chen's optimal three-stage design was used with a significant level of 0.05 and a power of 90% [28]. In the first stage, 13 patients were accrued, once two or more responses were observed, and then 10 more patients were accrued during the second stage. If there was a total of four more responses observed until the second stage, then 12 more patients were accrued. Thus, we planned to enroll at least 45 assessable patients. Time to progression, overall survival, and response duration were secondary end-points by the Kaplan-Meier analysis. Response duration was defined as the interval from the onset of response until evidence of progression. Time to progression and overall survival were calculated from the date of entry to the date of progression, and to the date of last follow-up or death, respectively.

Results

Characteristics of patients

The characteristics of the patients are presented in Table 1. Fifty were male and three were female. The median age was 53 years, with a range of 35 to 77 years. 69.8% of the patients (37/53) were ECOG performance 0–1. Twenty five patients were chemotherapy naïve,

Table 1 Clinical characteristics of patients

Characteristic		No. of patients
Male:Female		50:3
Age in years	Median (range)	53 (35–77)
Performance status (ECOG)	0–1/2	37/16
Previous treatment	Surgery/TACE[a]/None	4/24/25
Tumor node metastasis staging[b]	IIIA/IIIB/IIIC/IV	3/14/5/31
Okuda stage	I/II	27/26
Hepatitis virus status	HBs Ag+/ Anti-HCV+/None	43/4/6
Liver cirrhosis		49
Child classification	A/B	41/12
Alpha-Fetoprotein	Median (range)	372.8 (3.8–471174)
Pre-treatment laboratory data		
Bilirubin (mg/dl)	Median (range)	0.78 (0.16–2.10)
Albumin (g/dl)	Median (range)	3.45 (2.54–4.50)
Platelet count ($\times 10^3$/ml)	Median (range)	154.0 (61.0–438.0)
Portal vein thrombosis		21
Extrahepatic metastasis		
Lung		23
Lymph node		19
Bone		5
Other		6

[a] Transcatheter arterial chemoembolization
[b] Based on the American Joint Committee on Cancer tumor, node, metastasis (TNM) staging criteria (AJCC Cancer staging manual, sixth edition, 2002, published by Springer-Verlag New York, Inc)

Table 2 Responses to treatment

Response	No. of patients	Percentage
Complete response	0	0
Partial response	9	16.9
Stable disease	15	28.3
Progressive disease	26	49.1
Not assessable	3	5.7

whereas 24 patients were previously treated by transarterial chemoembolisation, and four patients had a surgery with curative intent. 58.5% of the patients (31/53) were stage IV, and lung was the most common site of extrahepatic metastasis. 92.4% of the patients (49/53) had liver cirrhosis and 43 patients were hepatitis B virus associated cirrhosis. Okuda stage was applied to the patients as previously described [29] and 27 patients were in stage I and 26 in stage II.

Responses and survival

Fifty of the 53 patients were evaluated for their response to treatment (Table 2). Three patients were withdrawn from the study before evaluation; two patients died of septic shock with febrile neutropenia and one patient was withdrawn after the first cycle because of hepatic toxicity. No patients achieved complete response, but nine had a partial response representing 16.9% of the overall objective response rate (95% confidence interval rate; 7.0–26.8%) with median response duration of 17.1 weeks (95% CI; 5.0–29.3 weeks, range; 7.1–51.7 weeks) based on intention-to-treat analysis. Fifteen patients had stable disease and the disease progressed in 26 patients. Therefore, 24 patients (45.2%) achieved disease stabilization with this treatment. Serum alpha-fetoprotein could not be used as a surrogate marker for response because nine patients showed baseline serum alpha-fetoprotein level within normal range (<20 ng/ml). However, serum alpha-fetoprotein level was changed parallel to tumor response in patients having increased level of serum alpha-fetoprotein. Thus, it was decreased in six patients with partial response and seven patients with stable disease showing less than 50% of decrease in tumor size. The median time for progression for the patients was 11.7 weeks (95% confidence interval; 6.2–17.2 weeks, range; 1.6–63.1 weeks). The median overall survival for the patients was 24.6 weeks (95% CI; 17.3–31.9 weeks, range; 3.0–131.3 weeks) (Fig. 1). In a univariate analysis, ECOG performance status less than one predicted a good response to treatment. Thus, when patients were dichotomized based on the performance status such as grade 0/1 and 2, good performance status was significantly related with responsiveness ($P=0.006$). Consistent with this result, presence of response and better performance status were associated with better overall survival ($P<0.01$); median survival of patients with PR and ECOG grade 0/1 was 41.7 weeks (95% CI; 31.8–51.6 weeks) and 26.3 weeks (95% CI; 20.9–31.7 weeks), respectively. However, other parameters including child classification, Okuda stage, and serum alpha-fetoprotein etc were not significantly associated with response and overall survival.

Toxicities and dose reductions

Of 149 courses of treatment (median 2; ranging 1–8), 148 courses were assessed for toxicity. The main toxicities encountered were hematologic toxicities including neutropenia (Table 3). Of the 53 patients, 17 patients (38.5%) experienced grade 3 or 4 neutropenia, and grade 3 or 4 thrombocytopenia was observed in five patients (9.4%). However, febrile neutropenia was observed in

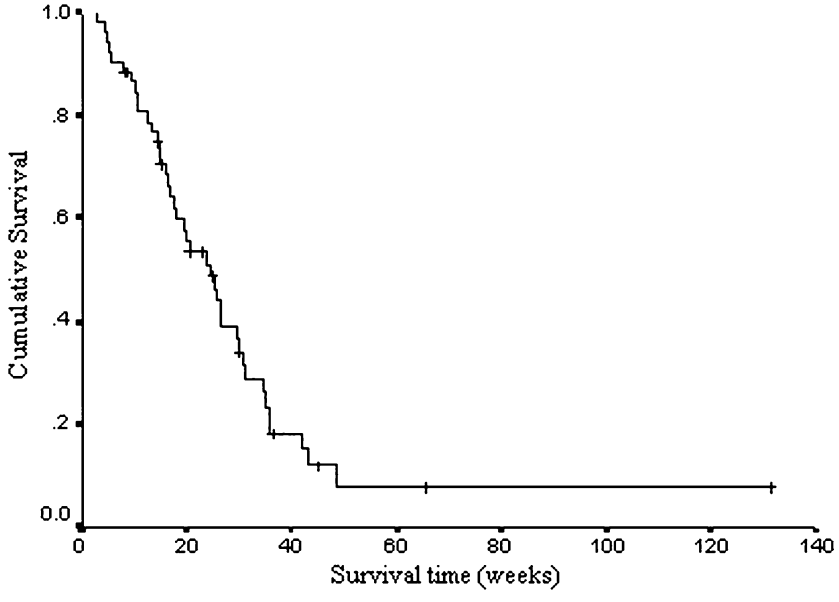

Fig. 1 Kaplan-Meier overall survival ($n=53$)

Table 3 Treatment related toxicity

Toxicity	Grade (% of cycles) ($n = 149$)		Grade (% of patients) ($n = 53$)	
	1–2	3–4	1–2	3–4
Hematologic toxicity				
Neutropenia	25(16.8)	19(12.7)	20(37.7)	17(32.1)
Anemia	13(8.7)	5(3.4)	8(15.1)	4(7.5)
Thrombocytopenia	12(8.1)	8(5.4)	9(16.9)	5(9.4)
Non-hematologic toxicity				
Alopecia	10(6.7)	1(0.7)	9(16.9)	1(1.8)
Hepatitis	11(7.4)	5(3.4)	10(18.9)	5(3.4)
Nausea/Vomiting	9(6.0)	1(0.7)	7(13.2)	1(1.8)
Diarrhea	7(4.7)	1(0.7)	7(13.2)	1(1.8)
Anorexia	3(2.0)	1(0.7)	2(3.8)	1(1.8)
Stomatitis	14(9.4)	5(3.4)	11(20.8)	5(3.4)
Fatigue	4(2.7)	2(1.3)	4(7.5)	2(3.8)

the five patients. Among five patients with febrile neutropenia, two patients died of neutropenia with septic shock after the first course of treatment. However, these two patients had liver function impairment designated as child class B and relative poor performance status (ECOG grade 2). Hepatic toxicity such as elevation of transaminase level or bilirubin was the common non-hematological toxicity; five patients showed grade 3 or 4. One patient experienced hepatic encephalopathy after the first course of treatment and the treatment was withdrawn in the case of this patient. Stomatitis was also common; five patients (3.4%) experienced grade 3 or 4, which caused subsequent dose reduction in UFT, and grade 3 or 4 nausea and vomiting developed in only one patient. Diarrhea was responded to by dosing delays and resumption of therapy after the diarrhea was resolved. Other treatment related side effects, including anorexia, nausea, vomiting, and fatigue were manageable. No significant cardiac toxicity was observed. The number of patients with at least one grade 3–4 adverse event attributable to study medication was 22 because some patients had both of hematologic and non-hamatologic toxicities. Dosage of epirubicin and cisplatin was reduced in these 22 patients. The dose intensity of epirubicin and cisplatin was as follows: epirubicin 10.575 mg/m^2/week (0.846 of planned dose intensity), and cisplatin 13.41 mg/m^2/week (0.894 of planned dose intensity). Twenty-four patients required dose reduction of UFT at least one course during the treatment. The most common cause of dose reduction for UFT was grade 3/4 stomatitis and nausea/vomiting. However, average dose intensity of UFT was 0.91 of planned dose intensity throughout the all courses of treatment.

Discussion

Although several chemotherapeutic agents such as doxorubicin, epirubicin, and cisplatin have demonstrated a consistent response rate of more than 10% when they are used in single-agent [14, 18, 30], there is no systemic chemotherapy that can be considered standard for advanced HCC, because no randomized trials have convinced that systemic chemotherapy improves survival over supportive care. In addition, there is no conclusive evidence showing superiority of combination chemotherapy to single-agent chemotherapy in advanced HCC. In our study, we achieved a 16.9% of response rate (95% confidence interval rate; 7.0–26.8%), with an additional 28.3% of patients achieving disease stability, based on intention-to-treat analysis. Therefore, epirubicin, cisplatin, and UFT moderated by leucovorin stabilized these tumors in 45.2% of the treated patients. This result can be compared with the previous phase II study combining epirubicin, cisplatin, and continuous infusion of 5-FU [26]. This regimen used the same dosage of epirubicin and cisplatin at day 1, and 5-FU was continuously infused for 24 h throughout the treatment course. They showed objective response rate of more than 20% [26]. However, the study population included 25 biliary tract tumors, thus only seven patients with HCC were enrolled and 2 patients showed partial response.

UFT has been reported to show good pharmacokinetics, which are similar to protracted intravenous injections of fluorouracil [31]. Furthermore, combination of DPD inhibitor, uracil may increase the anti-tumor effect of tegafur. Considering the fact that high levels of DPD are normally found in normal liver and HCC tissues, a substantial benefit of UFT can be expected in HCC. In spite of this theoretical rationale, the efficacy of UFT was reported to be disappointing in HCC when they were used in single-agent [32, 33], although administration of enteric-coated tegafur/uracil was reported to be effective for stage IV HCC [34]. However, the use of UFT in combination with other chemotherapeutic agents has not yet been investigated in HCC. Our study constitutes of the first report regarding the effects of UFT in combination with epirubicin and cisplatin as a treatment for HCC. Furthermore, it was demonstrated that UFT could be administered on an outpatient basis, thereby improving patients' convenience compared with the 5-FU administration protocol without comprising efficacy.

As for toxicity, our treatment regimen was relatively well tolerated despite the fact that a majority of patients

had liver cirrhosis. Hematologic toxicity was the most frequent cause of dose reduction. Grade 3–4 neutropenia was observed in 32.1% ($n = 17$) of patients, corresponding to 12.7% of total treatment courses. However, most hematologic toxicities of grade 3 or 4 recovered within two weeks with support from granulocyte colony-stimulating factor, and subsequent modifications of the dosage of epirubicin and cisplatin prevented the occurrence of serious neutropenia, allowing further treatment cycles. A previous similar regimen using cisplatin at the dose of 80 mg/m^2 for biliary tract tumors showed the substantial hematologic toxicity profile [35] and a recent phase II trial with continuous infusion of 5-fluorouracil, mitoxantrone, and cisplatin also had grade 3 and 4 neutropenia (71%), and thrombocytopenia (27%) [36]. Thus, the hematologic toxicity profile of our regimen can be acceptable. Non-hematologic toxicity was moderate, and gastrointestinal toxicities such as stomatitis or diarrhea were not observed at a significant frequency in this population. In addition, these non-hematologic toxicities were successfully managed with symptomatic treatment and treatment could be restarted after resolution of symptoms. This showed the advantage of oral administration of UFT, which can be discontinued whenever severe toxicity develops, and restarted after toxicity subsidence. Hepatic toxicity was another concern of our regimen because most patients had liver cirrhosis. Five patients showed hepatic toxicity greater than grade 3. However, subsequent chemotherapy was possible by dosage reduction and only one patient stopped further chemotherapy after the first cycle.

In conclusion, the combination of epirubicin, cisplatin, and UFT moderated by leucovorin showed modest anti-tumor activity with relatively tolerable toxicities and the objective response rate of this regimen was comparable to those found in other phase II studies. However, the survival benefit of this regimen is still unclear because it is possible that overall survival might be decreased as a result of toxicity. Therefore, a randomized phase III trial based on this regimen is warranted to clarify its survival benefit in patients with advanced HCC.

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