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ORIGINAL ARTICLE

Efficacy of combination chemotherapy with capecitabine plus cisplatin in patients with unresectable hepatocellular carcinoma

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Abstract
Purpose The aim was to assess the efficacy and safety of capecitabine (X) plus cisplatin (P) in patients with hepatocellular carcinoma (HCC).
Methods We retrospectively analyzed the data of 178 assessable among 195 consecutive HCC patients ineligible for curative therapy who were treated with XP at the National Cancer Center Korea between January 2002 and July 2007.
Results One patient (0.5%) had modified UICC stage II tumors, 12 (6.7%) had stage III, 51 (28.7%) had stage IVa, and 114 (64.1%) had stage IVb. The overall response rate was 19.7%, and 45.0% achieved tumor growth control. Tumor response and disease stability were significantly higher in patients with serum α-FP < 400 ng/mL, those with CLIP score ≤ 2, and those with a uninodular intrahepatic tumor or no residual intrahepatic tumor with extrahepatic tumors alone ($P < 0.05$). The median time to progression (TTP) and median overall survival were 2.8 months (95% CI 2.5–3.1 months) and 10.5 months (95% CI 7.9–13.1 months), respectively. Multivariate analyses showed that a uninodular or no residual intrahepatic tumor (hazard ratio, 0.524; $P = 0.006$) and female gender (hazard ratio, 0.539; $P = 0.019$) were independent predictors affecting TTP. Gastrointestinal symptoms were the most common grade 3 and 4 toxicities.
Conclusions Although XP chemotherapy produced moderate survival outcomes in advanced HCC patients, it was efficacious in the treatment of HCC patients with a uninodular or no residual intrahepatic tumor, especially women, regardless of extrahepatic tumor status.

Keywords Hepatocellular carcinoma · Capecitabine · Cisplatin · Response · Time to progression · Survival

Introduction

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer worldwide [1] and the third in Korea, accounting for 11.8% of cancers in Korea [2]. Although current screening modalities identify about one-third of the tumors at a potentially curable stage [3], many HCC patients present with advanced stage tumors at the time of diagnosis and have poor prognosis [4, 5]. Curative treatments of HCC, including surgical resection, liver transplantation and percutaneous interventions, are deemed suitable for only a small subset of patients [6]. Regrettably, transcatheter arterial chemoembolization (TACE), which has shown significant survival advantages compared with symptomatic treatment [7], is also of limited efficacy in the treatment of metastatic HCC. Advanced HCC is also highly resistant to most chemotherapeutic agents, and is rarely amenable to radiotherapy [8]. In addition, systemic treatments, such as interferon, hormonal therapy and cytotoxic chemotherapy, provide little survival benefit [4]. However, although the combination of capecitabine plus oxaliplatin (XELOX)

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showed an inferior overall response rate to that of gemcitabine plus oxaliplatin (GEMOX) (6 vs. 18%) in two recent phase II studies, both of them demonstrated durable stabilization of disease (72 vs. 76%) [9, 10].

Although sorafenib is the first agent ever to show survival benefit in patients with advanced HCC, sorafenib monotherapy may be insufficient to achieve satisfactory results in HCC patients [11]. Thus, to further improve the survival rates of patients with unresectable or metastatic HCC, new chemotherapy regimes based on a combination of molecular targeted agents are required.

Cisplatin alone and capecitabine alone have resulted in only modest overall response rates of advanced HCC (17, and 9 or 11%, respectively) [12–14], and although combination chemotherapy with doxorubicin, cisplatin and capecitabine achieved an encouraging overall response rate (24%) in 29 patients with metastatic HCC, severe hepatic dysfunction precluding further chemotherapy was observed in two patients [15]. The combination of capecitabine and cisplatin (XP) has shown promising antitumor activity with tolerable safety profiles in patients with advanced gastric cancer and biliary tract cancer [16, 17]. Furthermore, in a nude mouse model of HCC, platelet-derived endothelial cell growth factor identical to thymidine phosphorylase, by which capecitabine is converted to 5-fluorouracil (5-FU), was highly expressed in primary tumors and metastases, indicating that capecitabine may be beneficial in HCC patients [18]. In addition, capecitabine is orally administered, thereby avoiding the complications related to intravenous drug administration [19].

Based on these observations, we assessed the efficacy and tolerability of XP chemotherapy in 178 patients with unresectable or metastatic HCC and determined the factors predictive of response to this regimen.

Patients and methods

Patients

All patients diagnosed with HCC at the National Cancer Center in Goyang, South Korea between January 2002 and July 2007 were eligible for this study. The medical records of 195 consecutive HCC patients who were administered at least two cycles of XP chemotherapy between January 2002 and June 2007, identified via our computerized database, were retrospectively reviewed. Objective responses to treatment could not be evaluated in 17 patients owing to loss to follow-up, and these patients were therefore excluded. All of these 178 patients were deemed ineligible for higher-priority treatments such as surgical resection or TACE according to the guidelines of the Korean Liver Cancer Study Group and the National Cancer Center (Korea) [20] based on the Child–Pugh classification and modified International Union Against Cancer (UICC; Union Internationale Contre le Cancer) TNM staging system [21], and thus received systemic chemotherapy. XP was the first-line systemic chemotherapeutic regimen for 174 of the 178 patients. XP was offered regardless of whether patients had been treated previously with other chemotherapeutic agents or therapies such as resection, radiofrequency ablation (RFA), TACE or radiotherapy.

Except for biopsy-proven HCC, HCC diagnosis was made based on the guidelines of the Korean Liver Cancer Study Group and the National Cancer Center (Korea) [20, 22]. Under these criteria, a patient is diagnosed with HCC if he/she has one or more risk factors [hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or cirrhosis] and one of the following: a serum α-fetoprotein (α-FP) level of >400 ng/mL and a positive typical finding, which is indicative of arterial enhancement followed by venous washout in the delayed portal/venous phase, with at least one of the three imaging techniques (dynamic spiral computed tomography (CT), contrast-enhanced dynamic magnetic resonance imaging (MRI), or hepatic angiography); or a serum α-FP level of <400 ng/mL and positive typical findings with at least two of three imaging techniques. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, a Child–Pugh class of A or B, and a life expectancy of 12 weeks or more, and all provided written informed consent to treatment. Additional eligible criteria were absolute peripheral neutrophil count $\geq$ 1,200 mm^3, platelet count $\geq$ 50,000 mm^3, serum creatinine level $\leq$ 1.5 mg/dL, and total bilirubin level < 3.0 mg/dL.

Treatment schedule

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice a day according to the standard intermittent schedule (14 days of treatment followed by a 1- or 2-week rest period). Cisplatin was administered intravenously on days 1 and 8 at a dose of 30 mg/m^2 for 30 min with standard hydration. Treatment was repeated every 3 or 4 weeks and continued until disease progression or unacceptable toxicity, or until a patient refused further treatment. The dosage of the following cycle was reduced 25% for grade 3 or 4 toxicities. In addition, serotonin antagonists were routinely administered prior to cisplatin to prevent emesis, but prophylactic hematopoietic growth factors were not permitted. Before each chemotherapy cycle, patients underwent a physical examination, chest X-ray and laboratory evaluations, including a complete blood count; biochemical, hepatic and renal function tests; and α-FP level. Additionally, a dynamic spiral CT scan was performed after every two or three cycles of treatment.

Response and toxicity assessment

Tumor response was measured every two or three cycles until disease progression was observed by comparison of CT before and after treatment, and according to the new Response Evaluation Criteria in Solid Tumor (RECIST) [23]. Complete response (CR) was defined as disappearance of all viable tumors; partial response (PR) was defined as a ≥30% decrease in the sum of the longest diameters of viable tumors; progressive disease (PD) was defined as a ≥20% increase in the sum of the longest diameters of viable tumors, or the appearance of new tumors; and stable disease (SD) was defined as intermediate between PR and PD. Time to progression (TTP) was defined as time from the first day of treatment to disease progression, and overall survival (OS) was defined as time from the first day of treatment to death or end of follow-up. Toxicity was graded before initiation of a subsequent cycle based on the National Cancer Institute Common Toxicity Criteria, version 2.0.

Statistical analysis

All statistical analyses were performed using STATA software version 9.1 (StataCorp LP, College Station, TX, USA). All tests were based on a two-sided probability. The association between objective responses and clinical variables was assessed using χ^2 test or Fisher's exact test, if indicated. TTP and OS were estimated using the Kaplan–Meier method, and the log-rank test was used to compare TTP between groups. The Cox proportional hazards model was used to assess the independent predictors for TTP with adjustment for confounding variables. All variables with a $P < 0.20$ on univariate analysis were included in the subsequent multivariate analysis. Results were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

Baseline patient and tumor characteristics are summarized in Table 1. About 90% of patients were men, patient median age was 58 years (range, 30–80 years), and all patients had an ECOG performance status of 0–2. HCC was etiologically related to HBV in 139 (78.1%) patients, to HCV in 9 (5.1%), and to both in 4 (2.2%). In addition, 129 (72.5%) patients had liver cirrhosis, but all patients had good or modest hepatic function (Child–Pugh class A or B). Mild ascites was observed in 18.5% of patients, and splenomegaly in 71.3%. Over half of the patients had a CLIP score of 2 or less.

Table 1 Clinico-laboratorial characteristics at bsaseline

Characteristics	No. (%), $n = 178$
Sex	
Male	159 (89.3)
Female	19 (10.7)
Age (years)	
≥60	77 (43.4)
<60	101 (56.6)
Etiology of liver disease	
HBV	139 (78.1)
HCV	9 (5.1)
HBV + HCV	4 (2.2)
Other	26 (14.6)
ECOG performance status	
0	63 (35.4)
1	87 (48.9)
2	28 (15.7)
Child–Pugh class	
A	112 (62.9)
B	66 (37.1)
Liver cirrhosis	
Present	129 (72.5)
Absent	49 (27.5)
Ascites	
Present	33 (18.5)
Absent	145 (81.5)
Splenomegaly	
Present	127 (71.3)
Absent	51 (28.7)
CLIP score	
0	24 (13.5)
1	32 (18.0)
2	35 (19.7)
3	36 (20.2)
4	34 (19.1)
5	17 (9.5)
Intrahepatic tumor morphology	
No residual tumor[a]	26 (14.6)
Uninodular tumor[b]	15 (8.5)
Multinodular tumor[c]	75 (42.1)
Massive tumor[d]	62 (34.8)
Portal vein invasion	
Present	77 (43.3)
Absent	101 (56.7)
Nodal invaion	
Present	42 (23.6)
Absent	136 (76.4)
Distant metastasis	
Present	106 (59.6)
Absent	72 (40.4)

Table 1 continued

Characteristics	No. (%), *n* = 178
Metastasis site(s)[e]	
Lung	72 (64.3)
Bone	14 (12.5)
Peritoneum	10 (8.9)
Adrenal	12 (10.7)
Other	4 (3.6)
Modified UICC stage	
II	1 (0.5)
III	12 (6.7)
IVa	51 (28.7)
IVb	114 (64.1)
Prior treatment(s)[f]	
None	48 (20.3)
Surgery	31 (13.1)
RFA	4 (1.7)
TACE	111 (47.1)
Radiotherapy	38 (16.1)
Systemic chemotherapy	4 (1.7)
Laboratory parameters	
WBC (10^3 μL^{-1})	7.1 (2.24–15.81)
ANC (10^3 μL^{-1})	2.8 (1.2–11.5)
Hemoglobin (g/dL)	12.7 (10–15.3)
Platelets (10^3 μL^{-1})	186 (51–559)
Albumin (g/dL)	3.6 (2.7–4.9)
Total bilirubin (mg/dL)	0.7 (0.4–2.4)
ALP (IU/L)	145.5 (43–446)
AST (IU/L)	58 (14–184)
ALT (IU/L)	29 (82–186)
Creatinine (mg/dL)	1 (0.7–1.5)
Prothrombin time (INR)	1.1 (0.87–1.75)
α-FP (ng/mL)	215 (1.6–1,555,392)

Values are represented as No. (%) or median (range)

HBV hepatitis B virus, *HCV* hepatitis C virus, *ECOG* Eastern Cooperative Oncology Group, *RFA* radiofrequency ablation, *TACE* transcatheter arterial chemoembolization, *ANC* absolute neutrophil count, *IU* international unit, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *INR* international normalized ratio, *α-FP* alpha-fetoprotein

[a] No residual intrahepatic tumor with extrahepatic tumors alone

[b] Uninodular tumors with extension to ≤50% liver

[c] Multinodular tumors with extension to ≤50% liver

[d] Massive type tumors and tumors extending to >50% liver

[e] Eleven patients had two or more metastatic sites

[f] Fifty-seven patients received two or more kinds of prior treatments

When the disease was staged according to modified UICC staging criteria, we found that one patient (0.5%) had stage II tumors, 12 (6.7%) had stage III, 51 (28.7%) had stage IVa, and 114 (64.1%) had stage IVb. When categorized by intrahepatic tumor morphology (CLIP score) [24], 90 patients (50.6%) had a uni- or multinodular type of HCC limited to less than half the liver; 62 patients (34.8%) had HCC extending to over half the liver regardless of tumor morphology, or a massive type of HCC, including diffuse infiltrative HCC; and 26 patients (14.6%) had no residual intrahepatic tumor with extrahepatic tumors alone as a result of previous therapies, such as resection, RFA, or TACE. In addition, 77 patients (43.4%) had portal vein invasion, and 135 (75.8%) showed extrahepatic involvement of the tumor; these included 29 patients (16.3%) with nodal invasion and 93 (52.2%) with distant metastases, and 13 patients (7.3%) with both. Distant metastases were most commonly present in the lungs, and 11 patients (6.2%) had two or more metastatic sites. One hundred thirty patients (79.7%) had received prior treatments for HCC, with TACE being the most common. Four patients (1.7%) had received previous systemic chemotherapy regimens, including 5-FU plus cisplatin, 5-FU plus mitomycin, or gemcitabine alone. The clinical characteristics of the 17 excluded patients did not differ significantly from those of the 178 included patients.

With regard to baseline results of laboratory measurements, most median laboratory values were within normal range, although the median levels of alkaline phosphatase and aspartate aminotransferase were slightly high. The median level of α-FP was 215 ng/mL (range, 1.6–1,555,392 ng/mL).

Clinical efficacy

The median duration of follow-up was 9.1 months (range 1.4–68.5 months), and patients received a median of three cycles of treatment (range, 2–15 cycles). The results of clinical efficacy were listed in Table 2. We found that 6 patients (3.4%) achieved CR and 29 (16.3%) achieved PR, making the overall response rate 19.7%. These responses lasted from 1.3 to 34.2 months with a median of 6.3 months. Taking into account the 45 patients who had a best response of SD, with a median duration of 4.9 months (range, 1.2–27.9 months), the disease control rate was 45.0%. Table 3 shows the results of univariate analysis of parameters predictive of tumor response. The overall

Table 2 Antitumor response to treatment

Parameter	*n* = 178	
	No.	%
Complete response	6	3.4
Partial response	29	16.3
Stable disease	45	25.3
Progressive disease	98	55.0
Median No. of treatment cycles (range)	3 (2–15)	

response rates were significantly higher in patients with serum α-FP < 400 ng/mL ($P < 0.001$), those with CLIP score ≤ 2 ($P = 0.007$), those with a uninodular or no residual intrahepatic tumor ($P = 0.021$), and in women ($P = 0.047$). Tumor growth control was significantly higher in patients aged ≥60 years ($P = 0.025$), those with serum α-FP < 400 ng/mL ($P = 0.016$), those with CLIP score ≤ 2 ($P = 0.032$), and those with a uninodular or no residual intrahepatic tumor ($P = 0.008$). Patients without portal vein involvement had a better response, but the difference was not statistically significant. All other patient and tumor characteristics, including extrahepatic tumor status, were not associated with clinical efficacy.

Survival

The median TTP and median OS were, respectively, 2.8 months (95% CI 2.5–3.1 months) and 10.5 months (95% CI, 7.9–13.1 months; Fig. 1). The results of univariate analysis of factors predictive of TTP are listed in Table 4. TTP was significantly better in patients with a uninodular or no residual intrahepatic tumor ($P = 0.001$, Fig. 2a), a low score of CLIP ($P = 0.002$, Fig. 2b), no portal vein invasion ($P = 0.018$, Fig. 2c), and a low level of serum α-FP ($P = 0.022$, Fig. 2d), and was significantly higher in females than in males ($P = 0.037$; Fig. 2e). However, the presence or absence of extrahepatic tumor involvement had

Table 3 Response rate according to patient and tumor characteristics

Characteristics	Overall	Overall response rate			Disease control rate		
		No.	%	*P* value[e]	No.	%	*P* value[e]
All patients	178	35	19.7		80	45.0	
Age (years)				0.065			0.025
≥60	77	20	26.0		42	54.5	
<60	101	15	14.9		38	37.6	
Sex				0.047			0.092
Male	159	28	17.6		68	42.8	
Female	19	7	36.8		12	63.2	
Liver cirrhosis				0.318			0.742
Present	129	23	17.8		57	44.2	
Absent	49	12	24.5		23	46.9	
Child–Pugh class				0.265			0.789
A	112	25	22.3		50	44.6	
B	66	10	15.2		30	45.5	
Serum α-FP (ng/mL)				<0.001			0.016
≥400	89	6	6.7		32	36.0	
<400	89	29	32.6		48	53.9	
CLIP score				0.007			0.032
0–2	91	25	27.5		48	52.7	
3–5	87	10	11.5		32	36.8	
Intrahepatic tumor morphology				0.021			0.008
No residual tumor[a]	26	10	38.5		17	65.4	
Uninodular tumor[b]	15	5	33.3		9	60.0	
Multinodular tumor[c]	75	11	14.7		31	43.1	
Massive tumor[d]	62	9	14.5		23	37.1	
Extrahepatic tumor[f]				0.128			0.413
Present	135	30	22.2		62	45.9	
Absent	43	5	11.6		18	41.9	
Portal vein invasion				0.050			0.163
Present	77	10	13.0		31	40.3	
Absent	101	25	24.8		49	48.5	
Prior treatment(s)				0.853			0.886
Present	130	26	20.0		58	44.6	
Absent	48	9	18.8		22	45.8	

α-FP alpha-fetoprotein

[a] No residual intrahepatic tumor with extrahepatic tumors alone

[b] Uninodular tumors with extension to ≤50% liver

[c] Multinodular tumors with extension to ≤50% liver

[d] Massive type tumors or tumors extending to >50% liver

[e] Calculated using χ^2 test or Fisher's exact test

[f] Nodal invasion and/or distant metastasis

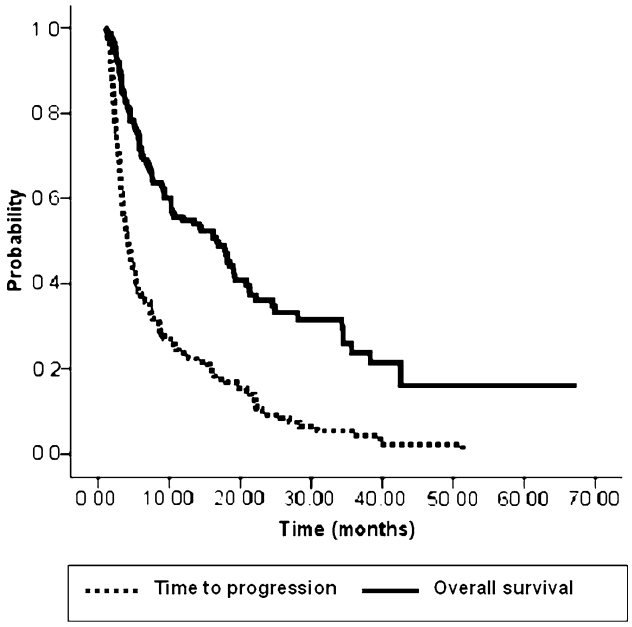

Fig. 1 Kaplan–Meier curves showing time to progression (*TTP*; *black dotted line*) and overall survival (*OS*; *black solid line*) rates for all patients ($n = 178$). The median TTP and median OS were 2.8 months (95% CI 2.5–3.1 months) and 10.5 months (95% CI 7.9–13.1 months), respectively

no influence on TTP. Multivariate analyses showed that a uninodular or no residual intrahepatic tumor (hazard ratio, 0.524; 95% CI, 0.331–0.831; $P = 0.006$) and female gender (hazard ratio, 0.539; 95% CI, 0.322–0.903; $P = 0.019$) were significant independent factors increasing TTP (Table 5).

Toxicity

There were no treatment-related deaths and all toxic effects were reversible. Most adverse effects were generally of grades 1 or 2. The most common grade 3 and 4 non-hematologic toxicities were gastrointestinal, including nausea/vomiting (9.6%) and diarrhea (4.5%), followed by hand–foot syndrome (3.9%). Grade 3 and 4 hepatic toxicities included hyperbilirubinemia and elevated alanine aminotransferase (ALT), which occurred in 4 (2.2%) and 2 (1.1%) patients, respectively. Although difficult to differentiate from cirrhosis-associated cytopenia, 13 patients (7.3%) experienced grade 3 or 4 neutropenia, whereas anemia was observed in only a single patient (0.6%; Table 6).

Discussion

In our cohort report of 1,078 patients with HCC, curative surgical resection was initially feasible in only 11.2% of patients and modified UICC stage I and II were 26.6% [25]. Most patients received palliative or conservative treatments, owing to the advanced stage of the tumor at the time of initial diagnosis. Of these palliative modalities, systemic chemotherapy may be crucial, however, there is no standard chemotherapeutic regimen that has shown considerable efficacy or survival benefit [26].

Table 4 Factors predicting time to progression (univariate analysis)

Variable	No. of patients	Median TTP (months)	95% CI	*P* value[e]
All patients	178	2.8	2.5–3.1	
Age (years)				0.090
≥60	77	3.2	1.9–4.5	
<60	101	2.5	2.2–2.8	
Sex				0.037
Male	159	2.6	2.3–2.9	
Female	19	6.0	4.7–7.3	
Liver cirrhosis				0.518
Present	129	2.7	2.3–3.1	
Absent	49	3.1	1.8–4.4	
Child–Pugh class				0.091
A	112	2.6	2.2–3.0	
B	66	2.9	2.3–3.5	
Serum α-FP (ng/mL)				0.022
≥400	89	2.4	2.1–2.7	
<400	89	3.7	2.7–4.7	
CLIP score				0.002
0–2	91	4.0	2.8–5.2	
3–5	87	2.4	2.1–2.7	
Intrahepatic tumor morphology				0.001
No residual tumor[a]	26	5.3	3.4–7.2	
Uninodular tumor[b]	15	4.2	0.6–7.8	
Multinodular tumor[c]	75	2.8	2.3–3.3	
Massive tumor[d]	62	2.5	2.1–2.9	
Extrahepatic tumor[f]				0.270
Present	135	2.9	2.2–3.6	
Absent	43	2.5	2.0–2.9	
Portal vein invasion				0.018
Present	77	2.5	2.0–3.0	
Absent	101	3.7	2.7–4.7	
Prior treatment(s)				0.243
Present	130	2.8	2.4–3.2	
Absent	48	2.4	1.3–3.7	

α-FP alpha-fetoprotein, *TTP* time to progression, *CI* confidence interval

[a] No residual intrahepatic tumor with extrahepatic tumors alone

[b] Uninodular tumors with extension to ≤50% liver

[c] Multinodular tumors with extension to ≤50% liver

[d] Massive type tumors or tumors extending to >50% liver

[e] Calculated using a log-rank test

[f] Nodal invasion and/or distant metastasis

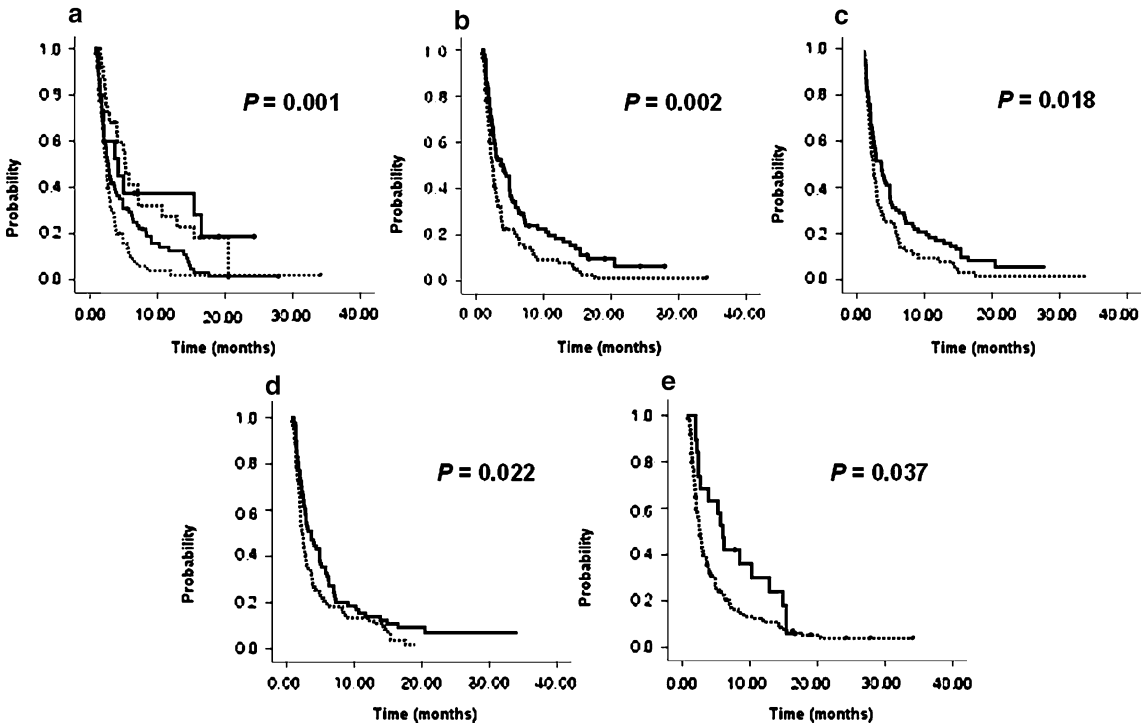

Fig. 2 Kaplan–Meier curves showing significant differences in time to progression (*TTP*) according to patient or tumor characteristics. Median TTP was significantly greater in patients with **a** a uninodular (*black solid line*) or no residual (*black dotted line*) intrahepatic HCC than in patients with multinodular (*gray solid line*) or massive (*gray dotted line*) HCC. In addition, patients with **b** CLIP score ≤ 2, **c** no portal vein invasion, or **d** serum α-FP < 400 ng/mL, and **e** female patients (*black solid line*) had significantly superior TTP compared with other patients (*black dotted line*). *P* values were calculated using a log-rank test

Since capecitabine and cisplatin have antitumor activities against HCC as single agents and their mechanisms of action do not overlap, we expected that the XP regimen would show synergistic or additive effects in patients with advanced HCC [17]. While the tumor growth control rate (45.0%) we observed with XP chemotherapy was relatively encouraging, the overall response rate (19.7%) was disappointing and was not superior to the rates observed with other regimens, especially doxorubicin plus XP regimen (24%) [15]. It is difficult, however, to directly compare our results with those of previous trials, owing to the heterogeneity of HCC and differences in patient and tumor characteristics. Over two-thirds of the HCC patients evaluated in this study had multinodular or massive types of intrahepatic tumors, and 92.8% of patients had far advanced tumors (modified UICC stage IVa or IVb). Moreover, considering the underlying liver cirrhosis and renal function in these patients, cisplatin 60 mg/m^2 was administered in divided doses on day 1 and 8, contrary to previous studies with a single dose on day 1. Hepatic dysfunction, which is often observed in patients with HCC, also did not significantly affect pharmacokinetics of capecitabine [27]. In addition, measuring response to treatment in HCC patients using RECIST [23] may have serious limitations. HCCs have unique factors, including variable tumor growth rates, the formation of small HCCs from dysplastic nodules despite the significant reduction of original tumor burden, and ill-defined diffuse tumor types, making it difficult to assess response to treatment using RECIST. Patients with diffuse infiltrative HCC were more likely to attain PD or at best SD. In addition, all patients who newly developed intrahepatic lesions were inevitably evaluated as having PD, despite any significant amelioration of originally preexisting local or distant lesions.

To our knowledge, the present study has the largest size (178 patients) of all the studies of chemotherapy in patients with HCC. We found that the 41 patients with a single nodular or no residual intrahepatic tumor showed an apparently favorable response or disease stability to XP chemotherapy. Almost all of these patients (97.6%), however, had extrahepatic tumor involvement, including 28 (68.3%) with distant metastases, 10 (24.4%) with nodal invasion, and 2 (4.9%) with both. Moreover, patients with multinodular or massive intrahepatic tumors, who had inferior responses to XP chemotherapy, had a significantly smaller incidence (69.3%) of extrahepatic tumor involvement, including nodal and/or distant metastasis, than did patients with a uninodular or no residual intrahepatic tumor ($P < 0.001$). These findings suggest that intrahepatic tumor status, rather than the presence or absence of nodal invasion and distant metastasis, is a

Table 5 Multivariate analysis of time to progression

Variable[e]	Time to progression	
	HR (95% CI)	*P* value[f]
Age (≥60 vs. <60 years)	1.325 (0.938–1.869)	0.110
Sex (male vs. female)	0.539 (0.322–0.903)	0.019
Child–Pugh class (A vs. B)	0.868 (0.615–1.226)	0.423
Serum α-FP (≥400 vs. <400 ng/mL)	0.804 (0.572–1.128)	0.207
Portal vein invasion (present vs. absent)	0.986 (0.685–1.420)	0.941
Intrahepatic tumor status (multinodular[c] or massive tumor[d] vs. no residual[a] or uninodular tumor[b])	0.524 (0.331–0.831)	0.006

HR hazard ratio, *CI* confidence interval, *TTP* time to progression, *α-FP* alpha-fetoprotein

[a] No residual intrahepatic tumor with extrahepatic tumors alone

[b] Uninodular tumors with extension to ≤50% liver

[c] Multinodular tumors with extension to ≤50% liver

[d] Massive type tumors or tumors extending to >50% liver

[e] All variables with a statistical probability of $P < 0.20$ on univariate analysis were included in multivariate analysis. Patients with no residual and those with uninodular intrahepatic tumors who presented with significantly better TTP on univariate analysis were compared with patients with multinodular or massive intrahepatic tumors

[f] Estimated from the Cox proportional hazards model

Table 6 Grade 3 and 4 adverse effects

Toxicity	*n* = 178	
	No. of patients	%
Non-hematological		
Nausea/vomiting	17	9.6
Diarrhea	8	4.5
Hand–foot syndrome	7	3.9
Stomatitis	5	2.8
Skin rash	3	1.7
Hyperbilirubinemia	4	2.2
ALT elevation	2	1.1
Hematological		
Leukopenia	5	2.8
Neutropenia	13	7.3
Anemia	1	0.6
Thrombocytopenia	8	4.5

ALT alanine aminotransferase

leading determinant of tumor responsiveness. Age- and gender-dependent responses were also observed although there was no statistical significance in the overall response rate of aged patients and the disease control rate of female patients.

In assessing the efficacy of HCC treatment, TTP should be given more weight than OS, since the mortality of HCC patients may be subject not only to the potency of antitumor therapy but to other factors, including underlying liver function, cirrhosis-related complications, the quality of supportive care and patient compliance. We observed a median TTP of 2.8 months, slightly lower than observed in previous trials (3.2–6.6 months), although these earlier trials did not specify tumor extent [9, 10, 28–30]. Nevertheless, our results suggest that the XP regimen has acceptable efficacy, especially since 92.8% of the patients in this study had UICC stage IVa or IVb with median survivals of 4.3 and 3.6 months, respectively [31]. Additional prospective trials are necessary to validate the better efficacy and usefulness of this regimen in HCC patients.

As expected, there was a correlation between TTP and intrahepatic tumor morphology or portal vein invasion, components of T (tumor) stage in UICC stage. Furthermore, using the Cox multivariate regression analyses, we were able to show that intrahepatic tumor status was an independent prognostic factor for TTP. That is, patients with a uninodular or no residual intrahepatic tumor had an approximately 47% reduced risk of disease progression. In contrast, extrahepatic tumor involvement, N or M stage, did not have a significant effect on TTP. This result indicates that, in HCC patients undergoing XP chemotherapy, T stage is more important to TTP than any other factor. Given this limited efficacy of XP chemotherapy, however, combination therapy with sorafenib or bevacizumab, which is a molecularly targeted agent, should be further investigated to obtain more extended benefits in the treatment of advanced HCC patients.

We found that the safety profile of the XP regimen was similar to profiles observed in other types of malignancies, although our use of lower dosages probably contributed to a milder toxicity. While grade 1 or 2 adverse effects were often observed, there were few serious toxicities. In particular, we found that the incidence of grade 3/4 hepatic dysfunction was much lower (2.2%) in our patients than in patients treated with doxorubicin plus XP (7%) [15]. In many patients, HCC is accompanied by underlying liver cirrhosis. Therefore, hematologic toxicity profiles caused by chemotherapy may be overestimated in HCC patients because of cirrhosis-associated cytopenia. We did not describe grade 1 or 2 toxicities in detail as they were liable to be underestimated due to the retrospective nature of this study. Capecitabine has a relatively low incidence of myelosuppression, and treatment with this agent may not worsen the cirrhosis-associated cytopenia caused by hypersplenism and liver dysfunction [13, 32]. In addition, capecitabine may be in harmony with combination regimens containing highly myelosuppressive agents such as cisplatin [12, 15].

In conclusion, we found that XP chemotherapy may be a beneficial therapeutic modality for the treatment of metastatic HCC patients with a uninodular or no residual intrahepatic tumor, especially women, who would be ineligible for curative or beneficial palliative treatments such as TACE. These results suggest that XP alone or in combination with TACE, local interventions, or targeted agents may be effective in treating metastatic lesions in HCC patients with controllable tumors in the liver parenchyma, despite the presence of nodal invasion or distant metastasis.

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