A Phase II study of 5-fluorouracil and cisplatin systemic chemotherapy for inoperable hepatocellular carcinoma with α fetoprotein as a predictive and prognostic marker

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Abstract. The objective of this study was to evaluate the efficacy and toxicity of 5-fluorouracil and cisplatin in patients with inoperable hepatocellular carcinoma (HCC), and to evaluate the utility of α fetoprotein (AFP) as a marker in assessing response to systemic chemotherapy. Fifty-seven inoperable HCC patients were enrolled. The administered regimen consisted of 60 mg/m^2 cisplatin on day 1 followed by 1,200 mg/m^2 5-fluorouracil on days 1-4, repeated every 3 weeks. One patient achieved a complete response (1.8%) and 7 a partial response (12.3%), an overall response rate of 14.1% and a disease control rate of 43.9%. Median time to progression (TTP) was 2.4 months, and median overall survival (OS) 9.8 months. The main grade 3 and 4 toxicities were leucopenia (10.5%), neutropenia (21.0%) and thrombocytopenia (8.8%). Of the 45 patients with an initially elevated AFP level, 15 (33.3%) showed a reduction of more than 50%. The disease control rate was significantly higher in AFP responders (80.0 vs. 23.3% in AFP non-responders, p<0.001), who moreover exhibited prolonged TTP (p=0.010). Combination chemotherapy of 5-fluorouracil and cisplatin showed modest disease control activity and acceptable toxicity in patients with inoperable HCC. Furthermore, AFP response may be a useful surrogate marker for clinical outcome.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, especially in Eastern Asia, where hepatitis B virus (HBV) is endemic. Moreover, despite improvements in screening methods, a significant number of patients are diagnosed at an inoperable advanced stage. The common reasons for inoperability are the presence of advanced cirrhosis, metastatic lesions, and invasion or thrombosis of the major blood vessels. Treatment options are often limited for these patients due to hepatic dysfunction and the limited efficacy of systemic chemotherapy. The disappointing results of systemic chemotherapy are possibly due to multidrug resistance gene expression, which is commonly observed in HCC (1,2). Consequently, the use of chemotherapy in HCC remains characterized by uncertainty regarding patient survival (3,4).

5-Fluorouracil (5-FU) is one of the chemotherapeutic agents most commonly used to treat HCC. Much interest has been shown in so-called 5-FU modulators, such as interferon and cisplatin, regarding their ability to increase the impact of 5-FU treatment (5-9). We therefore conducted a Phase II trial to evaluate the antitumor activity and toxicity of a systemic chemotherapy regimen based on 5-FU and cisplatin in patients with inoperable HCC.

Another problem associated with chemotherapy in HCC is the discrepancy between radiologic and biologic response. Leung *et al* (9) reported that patients with a radiologic partial response to chemotherapy achieved a pathologic complete response, meaning persistent lesions discerned by radiology may represent the complete pathologic resolution of viable tumor cells by chemotherapy. Thus, a traditional radiologic response does not always reflect the biologic response to chemotherapy in HCC. This difference in response might be overcome by combining radiography with the use of other markers that more accurately reflect tumor biology, such as serum α-fetoprotein (AFP).

AFP is currently used in chronic liver disease screening, although its utility as a predictive or prognostic marker is controversial (10-12). The aims of the present study were to evaluate the efficacy and toxicity of a combined 5-FU/cisplatin regimen in patients with inoperable HCC, and to determine whether AFP could serve as a predictive or prognostic marker of systemic chemotherapy.

Materials and methods

Patient population. From November 2001 to March 2005, 57 consecutive patients with inoperable HCC were enrolled in this study. Inoperability was due to metastatic lesions or portal

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vein thrombosis. Eligibility criteria included: i) pathologically confirmed HCC or an AFP level ≥400 ng/ml together with a hypervascular liver tumor and cirrhosis (13), ii) a bi-dimensionally measurable lesion, iii) ECOG (Eastern Cooperative Oncology Group) performance of 0-3, iv) Child-Pugh class A or B, and v) adequate bone marrow, hepatic and renal functions. Required laboratory data were as follows: absolute neutrophil count ≥1,500/m³, platelet count ≥50,000/m³, hemoglobin ≥10 g/dl, serum creatinine <1.5 mg/dl, total bilirubin <3.0 mg/dl and serum transaminase <2.5 times the normal level. Patients with an active infection or a concurrent major systemic disease were excluded. Patients who had progressed or relapsed after local therapy, such as surgery, transarterial chemoembolization (TACE) or percutaneous ethanol injection were included. Serum AFP levels were measured in all patients prior to chemotherapy.

Tumor response criteria. Computed tomography was routinely performed for HCC using a conventional two-phase technique (arterial phase and portal venous phase). Objective tumor response was evaluated using World Health Organization criteria (14) as follows: complete response (CR) was defined as the complete disappearance of all assessable lesions; partial response (PR) as a >50% reduction in the sum of the products of the longest perpendicular diameters of all the measurable lesions for a period of ≥4 weeks; stable disease (SD) as a <50% reduction or a <25% increase in the sum of the products of the longest perpendicular diameters of all the measurable lesions for a period of ≥4 weeks, and progressive disease (PD) a >25% increase in the area(s) of the original measurable lesion or the appearance of a new lesion. Computed tomography was checked after every two cycles of chemotherapy, unless there was definite evidence of disease progression. In patients who received TACE, compact lipiodol uptake lesions were considered to be necrotic (15) and were excluded from the measurable lesions for response evaluation.

To define the AFP response, we modified the tumor marker response criteria from CA-125 for ovarian cancer (16) and from prostate-specific antigen for prostate cancer (17), and evaluated the correlation between tumor marker (AFP) response and the clinical outcome of our patients. AFP responders were defined as patients showing a decline of >50% in one serum AFP level, confirmed by a second AFP level and lasting for more than 4 weeks. Patients with a <50% decline or a progressive AFP elevation were considered non-responders. Baseline AFP levels for these declines were measured within the 5 days prior to the start of chemotherapy.

Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0. Physical examinations and clinical manifestations, such as ascites and pain, were evaluated before treatment and during each chemotherapy cycle.

Treatment schedule. The 5-FU/cisplatin chemotherapeutic regimen consisted of 60 mg/m² cisplatin delivered as an intravenous infusion over 15 min on day 1, followed by 1,200 mg/m² 5-FU by continuous intravenous infusion over 10 h on days 1-4 repeated every 3 weeks. Treatment was discontinued for patients with progressive disease or for those who refused treatment.

Table I. Patient characteristics.

Characteristics (n=57)	No. of patients (%)
Median age (years)	53 (range 30-70)
Gender	
Male	48 (84.2)
Female	9 (15.8)
ECOG performance	
0-1	47 (82.5)
2	9 (15.8)
3	1 (1.8)
Etiology[a]	
HBV	45 (78.9)
HCV	4 (7.0)
Others	9 (15.8)
Previous treatment	
Transarterial chemoembolization	43 (75.4)
Hepatic resection	15 (26.3)
Liver transplantation	8 (14.0)
Metastatectomy	6 (10.5)
Radiation therapy	6 (10.5)
Percutaneous ethanol injection	7 (12.3)
None	9 (15.8)
Median no. of TACE	3 (range 1-13)
Child-Pugh class	
A	53 (93.0)
B	4 (7.0)
Portal vein thrombosis	
Yes	11 (19.3)
No	46 (80.7)
α fetoprotein (ng/ml)	Median 1,480
	(range 0-3,040,000)
<400	22 (38.6)
400-10,000	22 (38.6)
>10,000	13 (22.8)
Extrahepatic metastasis site	
Lung	37 (64.9)
Lymph node	11 (19.3)
Bone	9 (15.8)
Brain	2 (3.5)
Adrenal gland	2 (3.5)
Peritoneum	1 (1.8)

ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolization. [a]One patient had both HBV and HCV.

Statistical analysis. This trial was designed to test the null hypothesis that the response rate was at most 10% against the alternative hypothesis that it was at least 20%. A sample size of 57 patients provided 80% power to test this hypothesis, with a one-sided α-0.10.

Table II. Treatment-related toxicity (per patient).

Toxicity (NCI-CTC)	No. of patients (%)	
	Grade 1-2	Grade 3-4
Leucopenia	17 (29.8)	6 (10.5)
Neutropenia	14 (24.6)	12 (21.1)
Anemia	3 (5.3)	0 (0.0)
Thrombocytopenia	9 (15.8)	5 (8.8)
Nausea	15 (26.3)	3 (5.3)
Vomiting	9 (15.8)	0 (0.0)
Mucositis	4 (7.0)	1 (1.8)
Hepatotoxicity	6 (10.5)	3 (5.3)
Diarrhea	2 (3.5)	0 (0.0)
Neuropathy	2 (3.5)	0 (0.0)

Two patients developed febrile neutropenia and one died. NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Table III. Correlation between clinical variables and radiologic response rates.

Variables	No. of patients	Responders (RR %)	p-value
Gender			
Male	48	8 (16.7)	0.332
Female	9	0 (0.0)	
Age			
<55	32	3 (9.4)	0.280
≥55	25	5 (20.0)	
ECOG performance			
0-1	47	8 (17.0)	0.327
2-3	10	0 (0.0)	
Child-Pugh class			
A	53	7 (13.2)	0.464
B	4	1 (25.0)	
Portal vein thrombosis			
Yes	11	1 (9.1)	0.559
No	46	7 (15.2)	
α fetoprotein response			
Yes	15	5 (33.5)	0.012
No	30	1 (3.3)	

RR, response rate; ECOG, Eastern Cooperative Oncology Group.

The statistical analyses of 2x2 contingency tables of categorical variables were performed using the Pearson's χ^2 or the Fisher's exact test where appropriate. Time to progression (TTP) was determined as the interval between the initiation of chemotherapy and the date when disease progression was first documented. Overall survival (OS) was measured from the date of chemotherapy initiation to the date of death. Median TTP and OS were calculated using the Kaplan-Meier method. The associations of prognostic factors with survival were estimated with Cox's proportional hazard model. Multivariate analyses were carried out using a logistic regression model for response and Cox's proportional hazard models for TTP and OS. The potential prognostic factors (18) included for multivariate analyses were as follows: sex, age (<55 vs. ≥55 years), Child-Pugh class (A vs. B), performance (ECOG 0-1 vs. 2-3), portal vein thrombosis and AFP response. All values were two-sided, and statistical significance was defined as p<0.05. SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Tumor response and survival. From March 2003 to February 2006, a total of 57 patients (48 men and 9 women, median age 53 years, range 30-70) were enrolled in this study. The clinical characteristics of the patients are summarized in Table I. A total of 190 courses of 5-FU/cisplatin were delivered with a median number of 3 cycles per patient (range 1-8). Mean relative dose intensity was 75.2%. Twenty-five patients had pathologically-confirmed HCC, and the others were clinically diagnosed as described previously.

One patient achieved a complete response (1.8%) and 7 achieved partial responses (12.3%), an overall response rate of 14.1%. Seventeen patients reached stable disease (29.8%), and 32 experienced disease progression (56.1%), a disease control rate (CR+PR+SD) of 43.9%. The median duration of TTP was

2.4 months [95% confidence interval (CI), 1.6-3.3 months] and the median OS was 9.8 months (95% CI, 2.6-17.0 months). Fig. 1 shows the survival curves for TTP and OS.

Toxicity. The main grade 3 and 4 toxicities (per patient) were leucopenia (10.5%), neutropenia (21.0%), thrombocytopenia (8.8%) and transaminase elevation (5.3%) (Table II). Non-hematologic toxicities were mild and manageable. Two patients developed febrile neutropenia and one died. Spontaneous bacterial peritonitis occurred in one patient, but immediately improved after prompt antibiotic therapy. Toxicities were generally reversible and manageable.

Correlation between clinical variables and outcome. We conducted further analysis to ascertain predictive or prognostic factors and to identify the role of the AFP response in systemic chemotherapy. Correlations between clinical variables and radiologic response are documented in Table III. Only the AFP response was found to be significantly associated with radiologic response by univariate (p=0.012) and multivariate analysis (p=0.021; odds ratio=28.702; 95% CI, 1.676-491.538). The AFP response was the only independent predictive factor of response among the variables listed in Table III.

In terms of survival, radiologic response and AFP response were found to be significantly associated with TTP (hazard ratio=2.342; p=0.023 and hazard ratio=2.351; p=0.013,
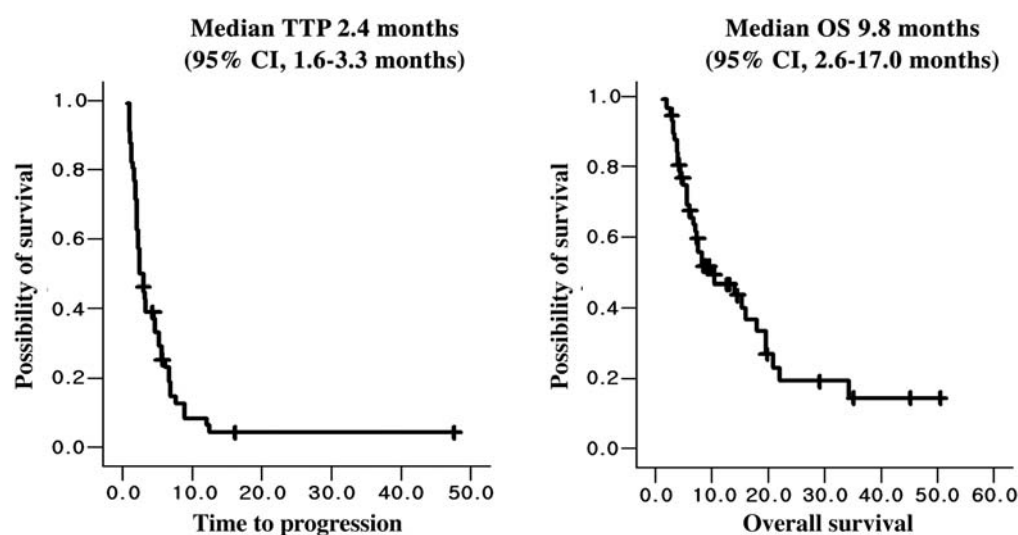
Figure 1. Kaplan-Meier analysis of time to progression (TTP) and overall survival (OS) in hepatocellular carcinoma.

Table IV. Correlation between clinical variables and time to progression.

	No. of patients	Median TTP (95% CI)[a]	Univariate analysis		Multivariate analysis	
			Hazard ratio (95% CI)[b]	p-value[b]	Hazard ratio (95% CI)[b]	p-value[b]
Gender						
Male	48	2.4 (1.3-3.5)	0.763 (0.370-1.576)	0.465	0.564 (0.217-1.465)	0.240
Female	9	2.8 (1.7-3.9)				
Age						
<55	32	2.4 (1.5-3.3)	0.841 (0.471-1.502)	0.559	0.827 (0.387-1.766)	0.624
≥55	25	3.1 (0.0-6.3)				
ECOG performance						
0-1	47	2.8 (2.0-3.7)	1.675 (0.801-3.497)	0.597	1.009 (0.378-2.695)	0.985
2-3	10	2.0 (1.1-2.9)				
Child-Pugh class						
A	53	2.4 (1.6-3.3)	1.445 (0.516-4.049)	0.483	2.623 (0.567-12.132)	0.217
B	4	1.6 (0.0-5.5)				
Portal vein thrombosis						
Yes	11	1.9 (1.0-2.8)	0.735 (0.366-1.475)	0.386	0.764 (0.325-1.794)	0.536
No	46	2.8 (1.9-3.7)				
α fetoprotein response						
Yes	15	5.4 (3.0-7.9)	2.351 (1.194-4.631)	0.013	2.569 (1.230-5.365)	0.012
No	30	2.0 (1.6-2.4)				
Radiologic response						
Yes	8	6.7 (3.6-9.7)	2.342 (0.135-0.865)	0.023		
No	49	2.2 (3.6-9.7)				

In multivariate analysis, the radiologic response was excluded due to its positive correlation with AFP response. A hazard ratio >1 can be thought of as the average increased risk of progression or dying at any point in time compared with the control group (described as above baseline). [a]Kaplan-Meier analysis; [b]Cox's proportional hazard model; TTP, time to progression measured in months; ECOG, Eastern Cooperative Oncology Group.

respectively) (Table IV). However, multivariate analysis indicated that only the AFP response was independently associated with a prolonged TTP (hazard ratio=2.569; 95% CI, 1.230-5.365; p=0.012). In OS, univariate analysis showed that portal vein thrombosis and performance were significantly associated with OS (hazard ratio=0.429; p=0.045 and hazard

Table V. Correlation between clinical variables and overall survival.

	No. of patients	Median OS (95% CI)[a]	Univariate analysis Hazard ratio (95% CI)[b]	Univariate analysis p-value[b]	Multivariate analysis Hazard ratio (95% CI)[b]	Multivariate analysis p-value[b]
Gender						
Male	48	8.1 (5.0-11.2)	0.840 (0.348-2.024)	0.697	0.434 (0.133-1.422)	0.168
Female	9	15.2 (1.7-28.7)				
Age						
<55	32	10.3 (0.3-20.3)	1.302 (0.680-2.494)	0.426	1.664 (0.746-3.712)	0.214
≥55	25	8.1 (0.0-16.3)				
ECOG performance						
0-1	47	13.9 (4.3-23.5)	2.336 (1.120-4.878)	0.024	2.182 (0.865-5.506)	0.098
2-3	10	6.0 (2.7-9.3)				
Child-Pugh class						
A	53	10.3 (3.1-17.6)	1.420 (0.335-6.024)	0.634	2.007 (0.347-11.610)	0.436
B	4	7.5 (0.0-15.8)				
Portal vein thrombosis						
Yes	11	4.4 (0.6-8.2)	0.429 (0.188-0.982)	0.045	0.729 (0.268-1.983)	0.536
No	46	13.9 (5.6-22.2)				
α fetoprotein response						
Yes	15	13.9 (2.5-25.3)	1.464 (0.668-3.118)	0.323	1.463 (0.650-3.291)	0.358
No	30	7.6 (0.7-14.5)				
Radiologic response						
Yes	8	Not reached	3.088 (0.740-12.866)	0.122		
No	49	8.1 (4.4-11.7)				

[a]Kaplan-Meier analysis; [b]Cox's proportional hazard model. OS, overall survival in months; ECOG, Eastern Cooperative Oncology Group.

ratio=2.336; p=0.024, respectively) (Table V), but multivariate analysis showed no statistical correlation between OS and potential prognostic variables.

AFP response and clinical outcomes. Of the 45 patients who initially had an elevated AFP level (>5 ng/ml), 15 (33.3%) showed an AFP reduction of >50% (mean reduction 76.4%), and 53.3% of these 15 responders showed this AFP reduction after the first cycle of chemotherapy.

The radiologic tumor response rates in AFP responders and non-responders were 33.3 and 3.3%, respectively (p=0.012) (Table VI). The sensitivity of the AFP response was 83.3% (5 of 6) and its specificity was 74.4% (29 of 39). The disease control rate was significantly higher in AFP responders (80.0% in AFP responders vs. 23.3% in AFP non-responders, p<0.001). TTP differed significantly for AFP responders and non-responders; median TTP was 5.4 months (95% CI, 3.0-7.9 months) in AFP responders and 2.0 months (95% CI, 1.6-2.4 months) in AFP non-responders (p=0.010). The median OS of AFP responders and non-responders was 13.9 months (95% CI, 2.5-25.3 months) and 7.6 months (95% CI, 0.7-14.5 months) (p=0.317). TTP and OS survival curves for AFP responders and non-responders are shown in Fig. 2.

Discussion

The antitumor activities of a number of chemotherapeutic agents against HCC remain poor; low response rates are often not reproducible, and consequently systemic chemotherapy has been shown to have a negligible effect on survival. However, some studies have indicated that aggressive chemotherapy may result in complete pathologic remission (9). Therefore, it is important that we continue to search for and develop more effective systemic chemotherapies, including novel agents.

In this study, we investigated the antitumor effect and toxicity of 5-FU/cisplatin combination chemotherapy. With an overall response rate of 14.1%, a disease control rate of 43.9% and a median OS of 9.8 months (95% CI, 2.6-17.0 months), our results compare favorably with those of chemotherapeutic regimens previously used in HCC. The mean relative dose intensity level was 75.2%, which was not higher than other chemotherapies in gastrointestinal cancer. This may have been caused by thrombocytopenia and leucopenia, which arose from underlying liver cirrhosis and sequestration at the spleen.

The response rate of this regimen was comparable to those of other Phase II studies of 5-FU-based combination chemotherapy, which ranged from 14.3 to 27.0% (7,9,19,20).

Table VI. Characteristics and clinical outcomes of α fetoprotein responders and non-responders.

| Characteristics (n=45) | No. of patients (%) | | p-value |
	AFP responders	AFP non-responders	
Median age (range)	51 (30-68)	55 (36-70)	0.769[c]
Gender			
Male	13 (86.7)	25 (73.3)	0.771
Female	2 (13.3)	5 (16.7)	
ECOG performance			
0-1	12 (80.0)	24 (80.0)	0.755
2	3 (20.0)	5 (16.7)	
3	0 (0.0)	1 (3.3)	
Etiology			
HBV	11 (73.3)	26 (89.7)	0.160
HCV	0 (0.0)	1 (3.4)	
Others	4 (26.7)	2 (6.9)	
Median no. of TACE	2 (range 1-10)	3 (range 1-13)	0.738[c]
Child-Pugh class			
A	14 (93.3)	28 (93.3)	1.000
B	1 (6.7)	2 (6.7)	
Portal vein thrombosis			
Yes	13 (86.7)	8 (26.7)	0.310
No	2 (13.3)	22 (73.3)	
α fetoprotein (ng/ml)			
<400	5 (33.3)	5 (16.7)	0.106
400-10,000	4 (26.7)	18 (60.0)	
>10,000	6 (40.0)	7 (23.3)	
Radiologic responder[a]	5 (33.3)	1 (3.3)	0.012
Non-responder	10 (66.7)	29 (96.7)	
Disease control[b]	12 (80.0)	7 (23.3)	<0.001
Progressive disease	3 (20.0)	23 (76.7)	
Median TTP (months) (95% CI)	5.4 (3.0-7.9)	2.0 (1.6-2.4)	0.010[d]
Median OS (months) (95% CI)	13.9 (2.5-25.3)	7.6 (0.7-14.5)	0.317[d]

[a]Radiologic responder, complete response + partial response. [b]Disease control, complete response + partial response + stable disease. p-values were based on the [c]Student t-test or [d]log rank test. Otherwise, p-values were based on the χ^2 test. AFP, α fetoprotein; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; TTP, time to progression; OS, overall survival.

However, because of the marginal antitumor activity of systemic chemotherapy, it is necessary to select patients who are likely to benefit from chemotherapy by identifying parameters that reflect response and prognosis. Serum AFP is one such promising surrogate marker, which is currently used to screen for early and operable stage HCC.

In the present study, the AFP response rate was 33.3%, which was identical to the previously-reported 32.4% (21), and AFP response was found to be significantly correlated with radiologic response. Multivariate analysis showed it to be an independent predictive marker of radiologic response (odds ratio, 28.702; p=0.021). AFP response was also associated with prolonged TTP by multivariate analysis (hazard ratio, 2.509; p=0.015), but not with OS. Moreover, AFP response was statistically more strongly associated with prolonged TTP than radiologic response. These findings suggest that even HCC patients who do not meet the criteria for radiographic tumor response may benefit from 5-FU/cisplatin chemotherapy in terms of TTP, if not OS. After disease progression, an abrupt rise in AFP was observed in the AFP responder group. This phenomenon suggests that, after the cessation of chemotherapy, the AFP responder group may have exhibited more aggressive biologic behavior than the AFP non-responder indolent group. In the present study, it appears that the small number of patients involved impeded clarification of the relation between AFP response and OS. In advanced HCC patients treated with thalidomide, a similar finding was observed; AFP response served as a prognostic marker of survival (22).
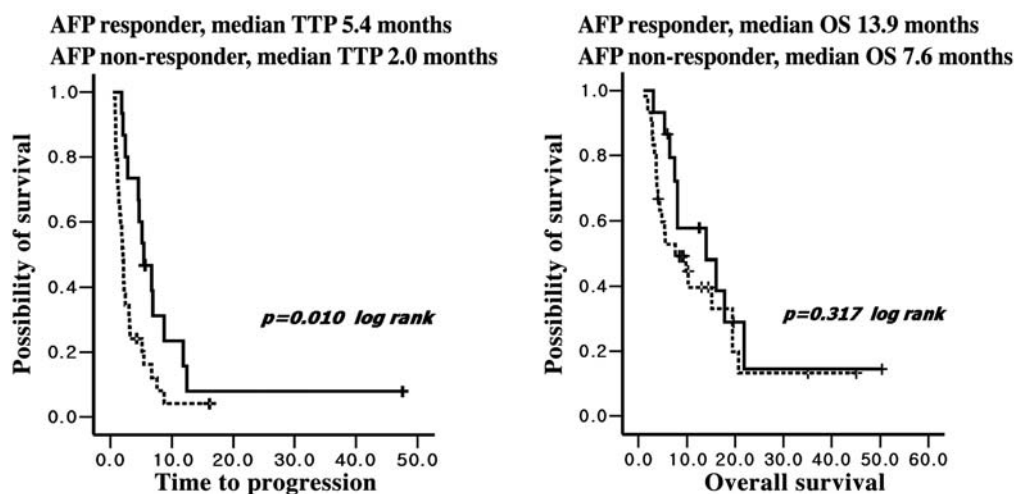
Figure 2. Kaplan-Meier analysis of time to progression (TTP) and overall survival (OS) in hepatocellular carcinoma patients with an elevated baseline α fetoprotein (AFP) response level. AFP responders, solid line; AFP non-responders, dotted line.

Moreover, in the present study, the majority of AFP responders (53.3%) showed a reduction in AFP after the first cycle of chemotherapy. This rapid decline implies that AFP has a possible role to play as an early response marker prior to follow-up computed tomography, and also suggests that AFP non-responders may not benefit from 5-FU/cisplatin chemotherapy. Consequently, it would be possible to avoid toxicity without clinical benefit.

It remains to be proved whether an AFP decline reflects the cell death of AFP-producing tumor cells, or whether it reflects the modulation of AFP production from tumor cells. However, there is a discrepancy between the radiologic and biologic responses in HCC (9), and an additional marker that could reflect biologic response would aid in the identification of those patients likely to benefit from chemotherapy. Further identification of the molecular, genetic and biological factors associated with AFP response is mandatory.

In terms of toxicity, the study regimen was tolerated. The spectrum of both hematologic and non-hematologic toxicity was reversible and manageable.

The present study was not without limitations. We did not measure another complementary tumor marker, such as protein induced by vitamin K absence or antagonist II (PIVKA-II). Our study population was relatively heterogeneous in terms of their previous treatments. Furthermore, a significant portion of the patients had already been heavily treated by locoregional treatments such as TACE (median no., 3). However, treatment with 5-FU/cisplatin showed a modest antitumor effect even in these heavily treated patients.

In conclusion, given a disease control rate of 43.9%, 5-FU/cisplatin chemotherapy appears to have modest disease control activity and acceptable toxicity in patients with inoperable HCC. The AFP response was found to be a useful predictive marker of response in HCC patients administered 5-FU/cisplatin, and was found to be an independent indicator of prolonged TTP. Thus, AFP response may reflect the biologic response more than the radiologic one. However, the observed limited prognostic reliability of AFP response for OS requires further investigation.

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