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Rapid and early α-fetoprotein and des-γ-carboxy prothrombin responses to initial arterial infusion chemotherapy predict treatment outcomes of advanced hepatocellular carcinoma

KENJI OYAMA[1], MASAHIKO KODA[2], TAKAAKI SUGIHARA[2], MANABU KISHINA[2], KENICHI MIYOSHI[2], TOSHIAKI OKAMOTO[2], MASANORI HODOTSUKA[2], YUKI FUJISE[2], TOMOMITSU MATONO[2], SHIHO TOKUNAGA[2], KINYA OKAMOTO[2], KEIKO HOSHO[2], JUNICHI OKANO[2] and YOSHIKAZU MURAWAKI[2]

[1]Tottori University Hospital Cancer Center; [2]Division of Medicine and Clinical Science, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8504, Japan

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Abstract. The aim of the present study was to predict the effects of transarterial infusion (TAI) chemotherapy based on early changes in α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) in patients with advanced hepatocellular carcinoma (HCC). Seventy-four patients who underwent TAI with cisplatin, 5-fluorouracil, mitomycin C and epirubicin for advanced HCC were enrolled. Antitumor responses were evaluated 6 months after TAI. Rapid and early responses were defined as the ratio of AFP or DCP after 1 week and 1 month compared to baseline. A total of 5, 10, 17 and 42 patients had complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), respectively. Early AFP response was significantly lower in the CR+PR compared to the SD+PD groups (P<0.01). The early DCP response was significantly lower in the CR+PR compared to the SD+PD. The sensitivity and specificity of rapid and early AFP responses in the CR+PR were 0.78 and 0.72, and 0.80 and 0.73, respectively, and those of rapid and early DCP responses were 0.67 and 0.65, and 0.77 and 0.71, respectively. The combination of AFP and DCP responses had higher specificity compared to AFP or DCP alone responses. Patients were divided into responder and non-responder groups to evaluate the prediction of survival outcome. Early responders of AFP, DCP and AFP+DCP, who were divided based on the cut-off values of CR+PR survived significantly longer than the non-responders (P<0.05). In conclusion, rapid or early responses of AFP and/or DCP levels 1 and 4 weeks after TAI chemotherapy helped to predict the treatment effects.

Correspondence to: Dr Masahiko Koda, Division of Medicine and Clinical Science, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, 36-1 Nishi-machi, Yonago, Tottori 683-8504, Japan
E-mail: masakoda@med.tottori-u.ac.jp

Key words: hepatocellular carcinoma, transarterial infusion chemotherapy, α-fetoprotein, des-γ-carboxy prothrombin, treatment response

Introduction

Hepatocellular carcinoma (HCC) is the fifth and seventh most common cancer in men and women, respectively (1) and the third leading cause of cancer mortality worldwide (2). Although radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), surgical resection and liver transplantation can be curative, ~80% of patients with HCC are not candidates for these strategies due to having advanced or metastatic disease at the time of presentation (3). Multiple advanced HCC has been treated using transcatheter arterial chemoembolization (TACE), but only in patients without portal vein tumor thrombus.

Sorafenib is a small molecular inhibitor of several tyrosine proteins and Raf kinases and is widely used to treat patients with advanced HCC with or without metastasis (4,5). Sorafenib is now recommended as it confers survival benefits beyond the best supportive care (6), but only patients with Child-Pugh A grade are candidates (7) due to the adverse events such as liver damage (8). Additionally, it is not widely administered as it is extremely expensive (9).

Patients with advanced HCC are often treated with transarterial infusion (TAI) chemotherapy according to indications. However, TAI has not yet been established as a standard treatment for advanced HCC without extrahepatic metastasis, as its effects have not yet been supported by concrete evidence generated from randomized controlled trials. Previous studies have identified complete (CR) and partial (PR) response rates after TAI of 27 to 40%, respectively (10,11) and a clearly improved prognosis for patients with stable (SD) or progressive disease (PD). However, repeated TAI for patients with SD or PD imposes physical, psychological and economic burdens. Therefore, patients with CR or PR should be differentiated from those with SD or PD during the earliest phase of the treatment.

α-Fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) are established tumor markers for HCC and they are useful for diagnosis (12,13). However, whether or not changes in their levels can serve as markers of responses to treatment remains controversial. Several recent studies have identified that changes in AFP levels following systemic chemotherapy, chemoembolization and radioembolization, may predict the

effects of treatment (14-16). Numerous studies have proven that AFP and DCP are useful not only as tumor markers, but also as prognostic factors for HCC (17,18).

Changes in tumor markers following anticancer therapies closely correlate with treatment effects in various types of solid tumors. Predicting treatment effects early will aid physicians in determining whether current therapy should be continued or changed.

However, correlations between AFP and DCP responses and survival outcomes in patients treated with TAI have not yet been established.

Therefore, the present study aimed to determine whether or not AFP and DCP responses during the early phase of treatment can predict the prognosis of patients with advanced HCC. Correlations were evaluated between AFP and DCP responses to treatment effects and survival rates in patients with HCC treated with TAI.

Materials and methods

Patients. A total of 74 patients with HCC confirmed by transcatheter arterial angiography and who received TAI comprising 25 mg cisplatin, 500 mg 5-fluorouracil, 6 mg mitomycin C and 30 mg epirubicin were enrolled at the Tottori University Hospital (Tottori, Japan) between January 2004 and December 2012. None of the patients were candidates for liver transplantation, surgical resection, PEI, RFA or TACE as multiple tumors were involved with one or both of the hepatic lobes with or without portal vein tumor thrombosis. Patients were treated with TAI once each month after initial infusion chemotherapy. Twenty-one patients received other treatments with subsequent TAI, and sorafenib was administered to two patients after repeated TAI. Fifteen patients succumbed within 6 months after initial TAI due to disease progression, and they were divided into PD. The study was approved by the Ethics Committee of the Tottori University Faculty of Medicine (no. 1863).

Protocols. Serum AFP and DCP levels were measured before the initial TAI at baseline and at 1 and 4 weeks after TAI. A rapid response rate was defined as the ratio of AFP or DCP value at 1 week after initial TAI compared to the baseline values and the early response rate was the ratio at 4 weeks. Serum AFP and DCP levels were measured using the Access AFP micro-particle enzyme immunoassay (Beckman Coulter, Brea, CA, USA) and Lumipulse presto PIVKA-II (Eidia Co., Ltd., Tokyo, Japan), respectively. Patients with normal baseline AFP (<10 ng/ml) and DCP (<40 mAU/ml) levels were excluded from the response evaluation. The effects of treatment and disease progression were assessed using contrast-enhanced computed tomography or magnetic resonance imaging every 8-12 weeks.

Response evaluation criteria. Antitumor responses were evaluated according to the standards of the Liver Cancer Study Group of Japan (19) at 6 months after the initial treatment. Briefly, a CR was defined as the total radiological absence of all the known lesions. A PR was defined as a decrease of ≥50% in the product of two perpendicular diameters of the largest tumor nodule for >4 weeks without the appearance of new lesions, or progression of existing lesions. A SD was defined as <50% decrease or not >25% increase in the product of two perpendicular diameters of the largest tumor nodule. A PD was defined as an increase of >25% in the product of two perpendicular diameters of the largest tumor nodule or one of the measurable lesions, or the appearance of new lesions. Patients who succumbed due to HCC progression before 6 months were categorized as having PD.

Statistical analysis. Data were statistically analyzed using Stat Flex version 6 (Artech, Osaka, Japan). A two-sided P<0.05 was considered to indicate a statistically significant difference. The amount of change in AFP and DCP between the CR and PR+SD+PD, and between the CR+PR and SD+PD groups was compared using the Mann-Whitney U test and categorical variables were compared using the Kruskal-Wallis test. Overall survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values were determined from receiver operating characteristic (ROC) curves.

Results

Antitumor responses at 6 months after TAI. Table I shows the characteristics of the patients. Among the enrolled patients, 5 (6.8%), 10 (13.5%), 17 (23.0%) and 42 (56.8%) achieved CR, PR, SD and PD, respectively. The objective response rate of overall (CR+PR) was 20.3%.

Survival outcomes according to treatment effects. Fig. 1 shows that the median overall survival of each group was 1,069, 1,201, 773 and 245 days for those who achieved CR, PR, SD and PD, respectively. Overall survival was longer for the CR compared to the PR+SD+PD group (P=0.054) and significantly longer for the CR+PR, compared to the SD+PD group (P=0.0005).

Comparison of clinical characteristics according to treatment effects. Table II shows the clinical characteristics of the patients in each group. Age, gender and rate of liver cirrhosis prior to the initial TAI did not significantly differ among the four groups at baseline. Median baseline levels of AFP and DCP did not significantly differ among these groups (P=0.07 and 0.86, respectively). In total, 8, 7, 7, 5, 3, 2 and 2 patients each were treated with PEI, low-dose FP, radiation therapy, TACE, TS-1 (tegafur-gimeracil-oteracil potassium), sorafenib and RFA, respectively. Twenty-one patients were treated using these approaches following repeated TAI and 11 were treated only with these approaches.

Rapid and early response indices. Fig. 2 shows the rapid and early response indices of AFP and DCP following initial TAI. The rapid AFP indices of median were 0.69, 0.83, 1.01 and 1.15 in CR, PR, SD and PD, respectively, and the early AFP response indices were 0.20, 0.51, 0.88 and 1.43 in CR, PR, SD and PD, respectively. The rapid AFP response index was lower in the CR compared to the PR+SD+PD group (P=0.0717) and in the CR+PR compared to the SD+PD group (P=0.0690). The early AFP response index was lower in the CR compared to the PR+SD+PD group (P=0.0099) and in the CR+PR compared to the SD+PD group (P=0.0003).

Table I. Patient characteristics.

Characteristics	Values
Age, median years (range)	67.7 (38-89)
Gender, n (male/female)	62/12
Etiology, n	
HBV	23
HCV	34
Alcohol	10
Others	7
Underlying liver disease, n	
Chronic hepatitis	26
Liver cirrhosis	48
Child-Pugh grade, n (A/B/C)	31/15/2
HCC clinical stage, n (II/III/IVa/IVb)	15/26/25/8
Portal vein tumor thrombus, n (%)	20 (27.0)
Hepatic vein tumor thrombus, n	1
Lymph node metastasis, n	6
Distant metastasis, n	
Lung	5
Bone	3
Adrenal gland	1
Serum markers at baseline, median (range)	
AFP, ng/ml	98 (11-162,579)
DCP, mAU/ml	542 (46-652,830)
Treatment following initial TAI, n	
TAI	29
TAI + others	21
Others	11
None	13
Treatment response, n (%)	
CR	5 (6.8)
PR	10 (13.5)
SD	17 (23.0)
PD	42 (56.8)
Survival outcome, n	
Succumbed	54
Alive	13
Unknown	7

HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; TAI, transarterial infusion; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

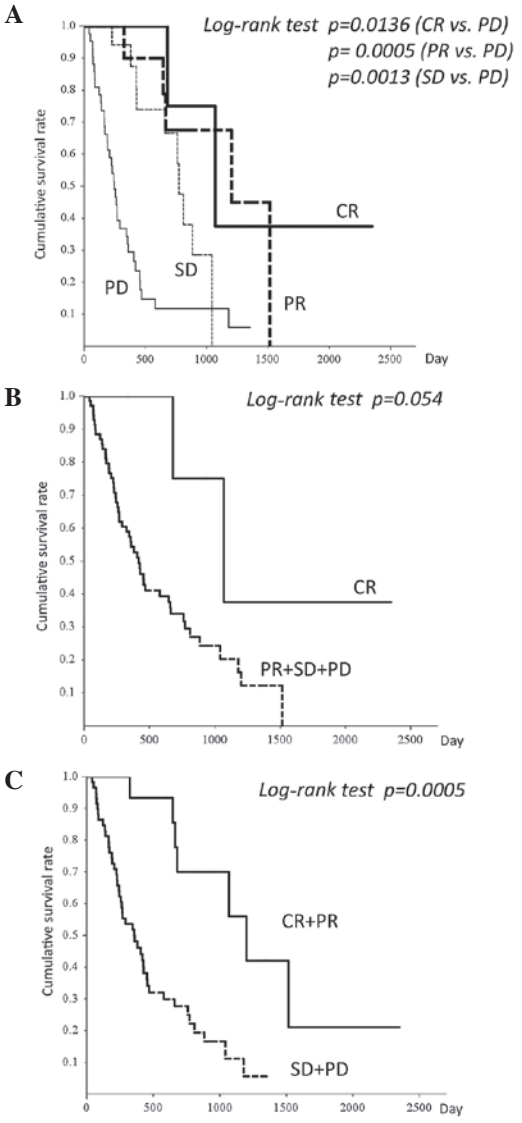

Figure 1. Kaplan-Meier analyses of overall survival according to objective responses. Overall survival was significantly shorter in (A) PD compared to the other groups (P<0.05) and longer for (B) CR compared to PR+SD+PD (P=0.054) and for (C) CR+PR compared to SD+PD (P=0.0005). PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

The rapid DCP response indices of median were 0.49, 1.22, 0.89 and 0.96 in CR, PR, SD and PD, respectively. The early DCP response indices were 0.12, 0.51, 0.63 and 1.14 in CR, PR, SD and PD, respectively. The rapid DCP response index was significantly lower in the CR compared to the PR+SD+PD group (P=0.0064). The early DCP response index was significantly lower in the CR, compared to the PR+SD+PD group and in the CR+PR, compared to the SD+PD group (P< 0.01).

Predicting performance based on the rapid and early response indices of AFP and DCP. Fig. 3 shows the ROC curves for treatment responses (CR vs. PR+SD+PD and CR+PR vs. SD+PD). The areas under the ROC curves of early AFP or DCP responses were larger for the CR than for the CR+PR group. The sensitivity and specificity for the CR group were 0.67 and 0.85 for a rapid AFP response (cut-off, 0.72), 1.00 and 0.89 for an early AFP response (cut-off, 0.46), 0.80 and 0.81 for a rapid DCP response (cut-off, 0.55) and 0.80 and 0.81 for an early DCP response (cut-off, 0.45), respectively. The sensitivity and specificity for the CR+PR groups were 0.78 and 0.72 for a rapid AFP response (cut-off, 0.92), 0.80 and 0.73 for an early AFP response (cut-off, 1.02), 0.67 and 0.65 for a rapid DCP response (cut-off, 0.77) and 0.77 and 0.71 for an early DCP response (cut-off, 0.61), respectively (Table III).

Table II. Patient characteristics according to treatment efficacy.

Characteristics	CR (n=5)	PR (n=10)	SD (n=17)	PD (n=42)	P-value
Age, years	66.8±11.5	66.8±11.4	70.0±9.1	67.1±12.2	0.86
Gender, n (male/female)	5/0	9/1	15/2	33/9	0.51
Etiology of liver disease, n					
alcohol/B/C/others	0/3/2/0	1/5/3/1	5/3/7/2	4/12/22/4	
Liver cirrhosis, n (no/yes)	1/4	4/6	7/10	14/28	0.82
Clinical stage, n (II/III/IVa/IVb)	1/2/2/0	3/3/4/0	5/7/4/1	6/14/15/7	
Baseline tumor markers, median (range)					
AFP, ng/ml	395 (46-70,254)	49 (13-35,730)	20 (11-53,110)	270 (11-162,579)	0.07
DCP, mAU/ml	360 (102-18,753)	2,010 (46-9,342)	425 (53-32,652)	598 (46-652,830)	0.86
Following treatment, n					
TAI/TAI + others/others/none	2/3/0/0	4/4/2/0	11/5/1/0	12/9/8/13	

TAI, transarterial infusion; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin.

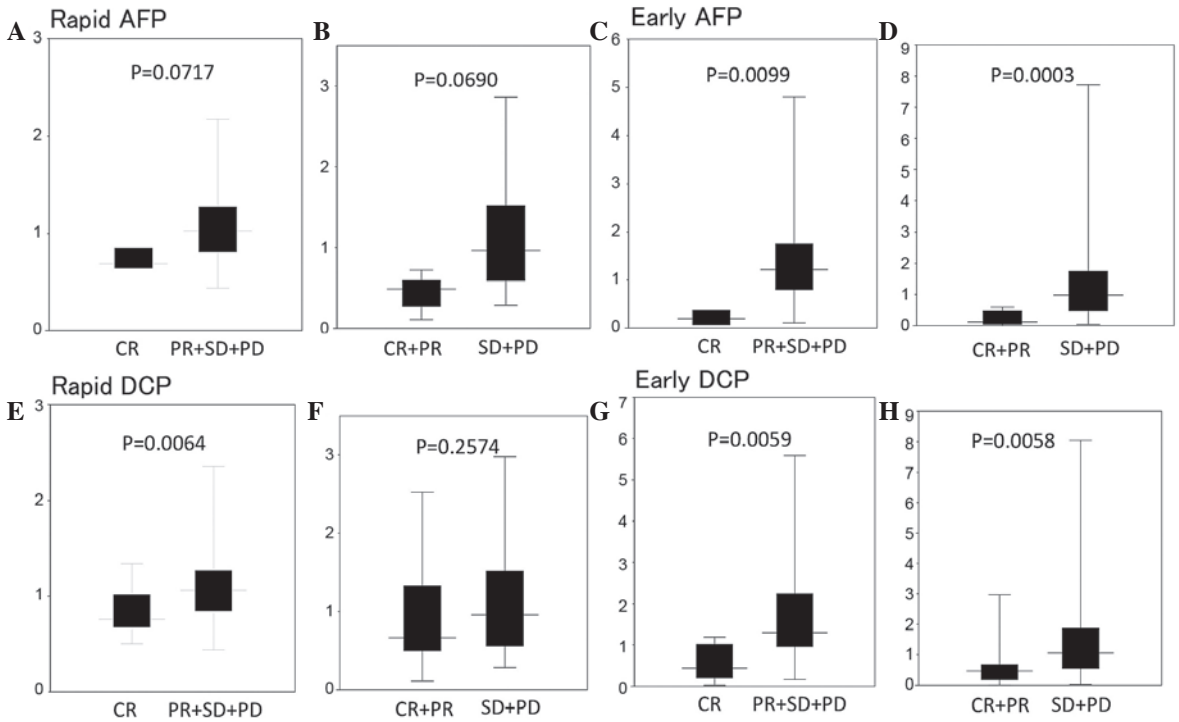

Figure 2. Rapid and early response indices of AFP and DCP following initial TAI. (A-D) Rapid and early AFP responses were lower in CR or CR+PR compared to PR+SD+PD or SD+PD. (E and F) Rapid DCP response was significantly lower in CR compared to PR+SD+PD. (G and H) Early DCP responses were significantly lower in CR or CR+PR compared to PR+SD+PD or SD+PD. AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; TAI, transarterial infusion; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

Predicting performance based on a combination of AFP and DCP. Combining the AFP and DCP responses markedly increased the ability to predict CR and CR+PR compared with each marker alone (Table IV). The cut-off values of AFP and DCP were the same as those used for the single marker analysis. The sensitivity and specificity were 0.67 and 0.98 for a rapid response, 1.00 and 1.00 for an early response for the CR group, 0.63 and 0.88 for a rapid response, and 0.75 and 0.88 for an early response, respectively, for the CR+PR group. The PPVs of rapid and early responses for CR were 0.67 and 1.00, and those for CR+PR were 0.50 and 0.55, respectively.

Antitumor responses and survival outcomes according to subsequent treatments following initial TAI. The objective response rate of repeated TAI, repeated TAI + others and others as subsequent treatments were 20.7, 33.3 and 18.2%, respectively. The median overall survival of each group was 659, 646, 418 and 140 days for those who received repeated TAI, repeated

Table III. Predicting performance by AFP or DCP.

Characteristics	Cut-off value	Sensitivity	Specificity	PPV	NPV	Hazard ratio	AUROC
AFP							
Rapid							
CR	0.72	0.67	0.85	0.20	0.98	11.3	0.81
CR+PR	0.92	0.78	0.72	0.35	0.94	9.2	0.69
Early							
CR	0.46	1.00	0.89	0.33	1.00	NA	0.95
CR+PR	1.02	0.80	0.73	0.38	0.95	10.8	0.87
DCP							
Rapid							
CR	0.55	0.80	0.81	0.29	0.98	17.2	0.87
CR+PR	0.77	0.67	0.65	0.33	0.88	3.8	0.61
Early							
CR	0.45	0.80	0.81	0.27	0.98	16.7	0.87
CR+PR	0.61	0.77	0.71	0.42	0.92	8.3	0.75

PPV, positive predictive value; NPV, negative predictive value; AUROC, area under receiver operating curve; PR, partial response; CR, complete response; NA, not applicable.

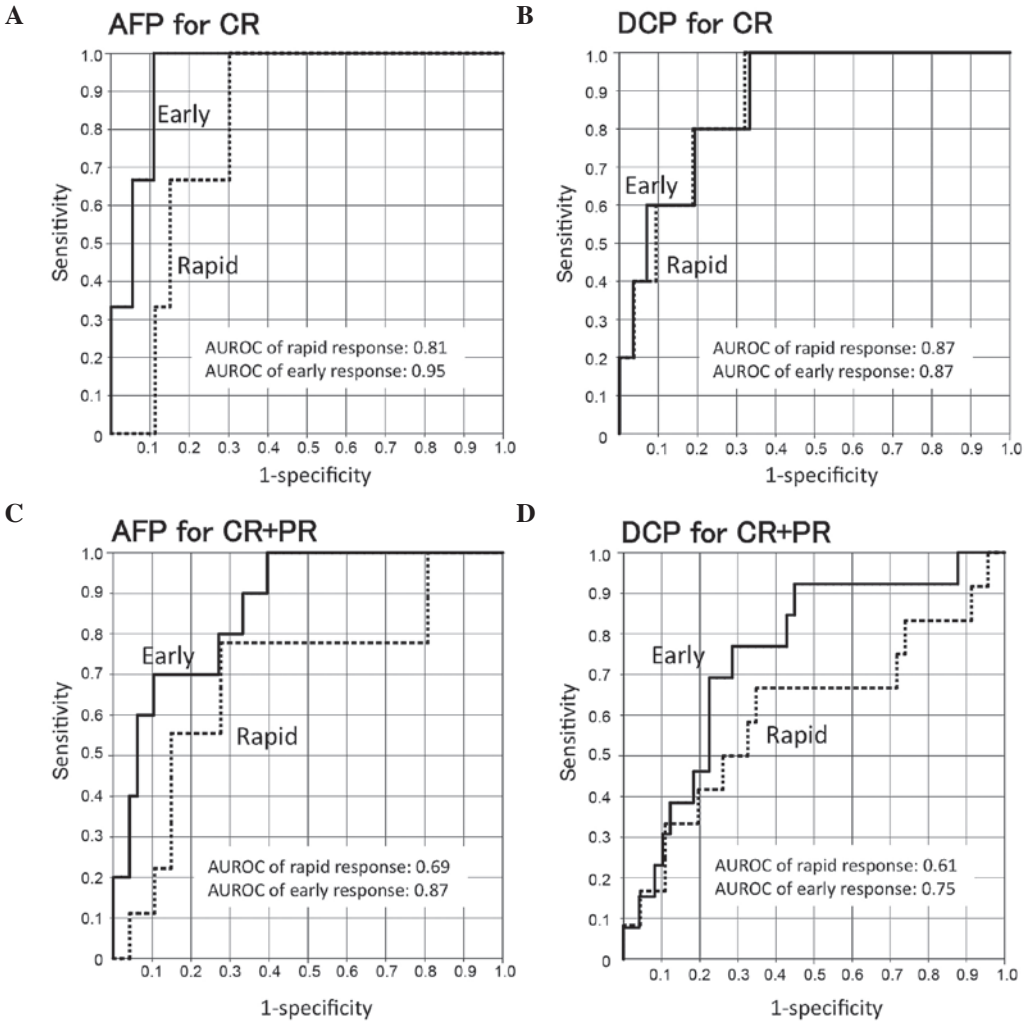

Figure 3. ROC curves of rapid and early response indices of AFP and DCP. Areas under ROC curves for early AFP or DCP responses were larger than those of rapid responses in the CR or CR+PR group (A-D), but were not significant. AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; AUROC, area under receiver operating curve; PR, partial response; CR, complete response.

Table IV. Predicting performance by combination of AFP and DCP.

Characteristics	Sensitivity	Specificity	PPV	NPV	Hazard ratio
Rapid AFP+DCP					
CR	0.67	0.98	0.67	0.98	88.0
CR+PR	0.63	0.88	0.50	0.92	11.6
Early AFP+DCP					
CR	1.00	1.00	1.00	1.00	NA
CR+PR	0.75	0.88	0.55	0.95	21.6

PPV, positive predictive value; NPV, negative predictive value; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; NA, not applicable; PR, partial response; CR, complete response.

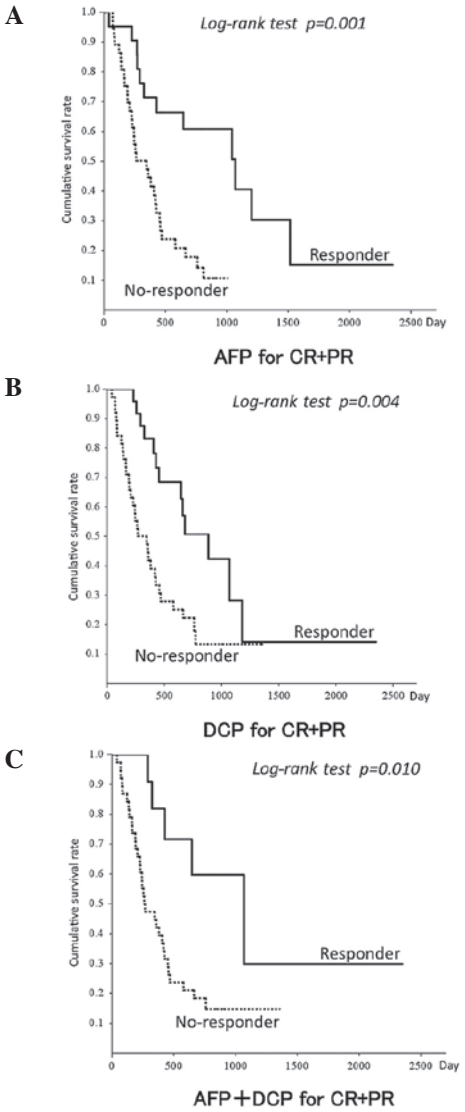

Figure 4. Kaplan-Meier analyses of overall survival according to AFP and DCP responses. (A) Early responders of AFP, (B) DCP and (C) AFP+DCP as predicting CR+PR survived significantly longer compared to non-responders. AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; PR, partial response; CR, complete response.

Table V. Survival outcomes according to AFP and DCP responses.

Characteristics	Median survival time, days	P-value
AFP		
Rapid		
CR responder/non responder	345/405	0.146
CR+PR responder/non responder	380/291	0.667
Early		
CR responder/non responder	359/1,069	0.015
CR+PR responder/non responder	345/1,069	0.001
DCP		
Rapid		
CR responder/non responder	359/453	0.402
CR+PR responder/non responder	269/456	0.150
Early		
CR responder/non responder	380/884	0.056
CR+PR responder/non responder	269/884	0.004
AFP+DCP		
Rapid		
CR responder/non responder	345/>2,000	0.113
CR+PR responder/non responder	324/646	0.134
Early		
CR responder/non responder	345/1,069	0.062
CR+PR responder/non responder	262/1,069	0.010

AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; NA, not applicable; PR, partial response; CR, complete response.

TAI + others, others and no treatment following initial TAI, respectively. All the patients without subsequent treatment had PD. Survival outcome in patients without subsequent treatment was significantly low compared to other treatments (data not shown, P<0.01). There were no significant differences between repeated TAI, repeated TAI + others and others.

Survival outcomes according to AFP and DCP responses. Based on the cut-off values of CR and CR+PR, patients were divided into responder and non-responder groups to evaluate the prediction of survival outcome (Fig. 4, Table V). Early

responders of AFP and AFP+DCP for predicting CR survived significantly longer than non-responders (P<0.05). Early responders of AFP, DCP and AFP+DCP in predicting CR+PR survived significantly longer than non-responders (P<0.05). Rapid responders of AFP, DCP and AFP+DCP were not significantly different from non-responders with regards to survival.

Discussion

Patients with advanced HCC who had early AFP and DCP responses following initial TAI had significantly improved treatment effects and longer overall survival than those without AFP and DCP responses.

AFP is secreted in ~70% of patients with HCC and it is frequently measured in clinical practice for diagnosis or pretreatment prognosis, but the predictive or prognostic significance of the AFP response during treatment has not been evaluated frequently. DCP was also used as a tumor marker of HCC and was more likely to be elevated in patients with advanced HCCs, such as vascular invasion or distant metastasis (20). Investigators have proposed a role for tumor marker dynamics during surgical treatment, more specifically, that a change in AFP or DCP can predict prognosis or recurrence following surgical resection (21-23). However, the AFP and/or DCP responses have not been assessed in patients treated with TAI.

Three recent studies of patients with advanced HCC who received various types of systemic therapy, such as thalidomide (24), doxorubicin-based combination chemotherapy (15) and chemotherapy with or without molecularly targeted therapies (14), concluded that a change in AFP during treatment is a useful surrogate for predicting treatment effects and the survival rate of patients. The criteria for an AFP response have various definitions according to treatment modalities that affect AFP responses in different ways. Riaz *et al* (16) and Vora *et al* (14) defined an AFP response as >50% reduction from baseline for locoregional therapy and systemic chemotherapy, whereas Chan *et al* (15) defined it as >20% reduction in systemic chemotherapy. The present study identified that the rapid AFP and DCP responses in CR were 31 and 51% decreased from baseline, respectively. Early AFP and DCP responses in the same group were 80 and 88%, respectively. These data were appropriate considering that the half-lives of AFP and DCP are 6 and 3.2 days, respectively (25).

Serum AFP and DCP levels have been routinely measured in the clinical setting for decades and they can be immediately, easily and broadly monitored in outpatient clinics as a potential surrogate for the effects of treatment in patients with advanced HCC. The present study found that the early AFP response was most sensitive for predicting CR and the sensitivity of rapid DCP for this group was 80%. Early responders of AFP, DCP and a combination of these markers were shown to have improved survival outcomes than non-responders. To the best of our knowledge, this is the earliest time point used in similar studies and it was apparently the most relevant to the clinical treatment of advanced HCC. Treatment effects may be more accurately predicted at 1 month after the initial TAI as the areas under the ROC curves for AFP or DCP were larger for early, compared to the rapid responses.

The combination of AFP and DCP responses markedly increased the ability to predict CR and CR+PR compared to each marker alone. One explanation may be that 2 of the 5 patients who achieved CR and 5 of 10 who achieved PR had high baseline values of either AFP or DCP.

A biomarker that can be detected during the early phase of treatment is valuable, as it may help to identify a subgroup of patients with a poor prognosis who would thus be candidates for other treatment strategies. Subsequent treatment methods following initial TAI except for no treatment did not affect treatment outcomes in terms of overall survival rate in the present study. Indeed, the predicting performance for all the treatments was similar to that for subsequent repeated TAI. At the advanced stage of HCC, multidisciplinary and personalized therapy was required. From this view point, predicting treatment outcomes in the early period following initial TAI is extremely important. The present results may aid physicians to accurately determine disease courses and establish further treatment plans following completion of the initial TAI. Thus, adding other types of systemic therapy, such as sorafenib, should be considered if possible at an earlier stage of treatment for patients with little or no AFP and DCP responses.

Several studies have examined the predictive roles of AFP and DCP responses (26-28), but the present findings are important for several reasons. First, to the best of our knowledge, only a few studies have simultaneously evaluated the clinical value of AFP and DCP responses through correlations with clinical outcomes in patients who were treated with homogeneous TAI protocols. Second, tumor markers were evaluated at an earlier time point than similar studies.

The potential limitations of the present study included a relatively small and less homogeneous patient population. AFP and DCP levels were measured only at baseline and at 1 and 4 weeks following TAI. Validation study in larger patient cohorts and/or with more stringent criteria for early AFP and DCP responses may help to verify the usefulness of such an approach.

In conclusion, early AFP and DCP responses appear to be significant predictors of the effects of TAI and the survival of patients with advanced HCC. Levels of AFP and DCP, particularly during the early phase of treatment, should be further explored in larger clinical studies.

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