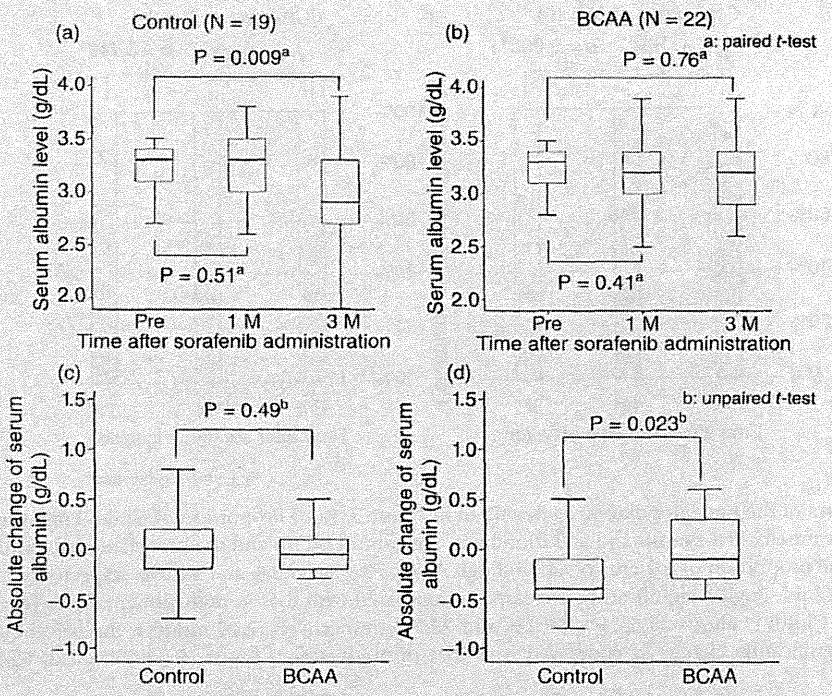

Figure 3 Subgroup analyses of 41 patients who took sorafenib for >1 month with no anticancer therapies other than sorafenib and who could be observed for ≥3 months after sorafenib administration. They involved 22 branched-chain amino acid (BCAA) group patients and 19 control group patients. (a,b) Changes in serum levels of albumin in the two groups. Three months after sorafenib administration, serum levels of albumin decreased significantly compared with pretreatment levels in the control group ($P = 0.009$), whereas in the BCAA group, serum levels of albumin did not decrease significantly from baseline ($P = 0.076$). Box plots of (c) δ1 and (d) δ3 in the two groups. Although there is no significant difference between δ1 of the BCAA group and that of the control group ($P = 0.49$), there is a significant difference between the two groups in terms of δ3 (median δ3; BCAA group vs control group = −0.1 vs −0.4, $P = 0.023$). δ1 and δ3 are defined as: δ1 = (serum level of albumin 1 month after sorafenib therapy started) − (pretreatment serum level of albumin), δ3 = (serum level of albumin 3 months after sorafenib therapy started) − (pretreatment serum level of albumin).

treated with sorafenib. Indeed, we often care for patients who fail to continue sorafenib therapy owing to malnutrition or a decreased serum level of albumin and ascites even in patients with a pretreatment liver function of Child–Pugh class A.[19,20] However, there have been no reports focusing on plans for maintaining liver function during sorafenib therapy, hence the reasons for the current comparative study. This is the first report looking at the efficacy of BCAA granules during sorafenib therapy.

A significant difference between the BCAA group and control group was observed in terms of absolute change in serum levels of albumin and Child–Pugh classification 3 months after sorafenib therapy. BCAA supplementation has been reported to prevent the decrease in serum levels of albumin after several interventions for HCC such as surgery, TACE or RFA.[14,15,18] Our results are in agreement with those reports of the efficacy of BCAA supplementation. In addition, in view of the results of the present study and previous reports,[9,12,13] BCAA treatment seems to exert effects on serum levels of albumin over longer periods (months).

Comparing the BCAA group and control group, a significant difference was noted in the administration period of sorafenib and OS, as well as marginal significance in the total dose of sorafenib. Moreover, BCAA treatment was a significant favorable predictor associated with OS with a hazard ratio of 2.36 in our multivariate analysis. These results suggest that BCAA granules can prevent decreases in the serum level of albumin during sorafenib therapy, resulting in a prolonged administration period of sorafenib and

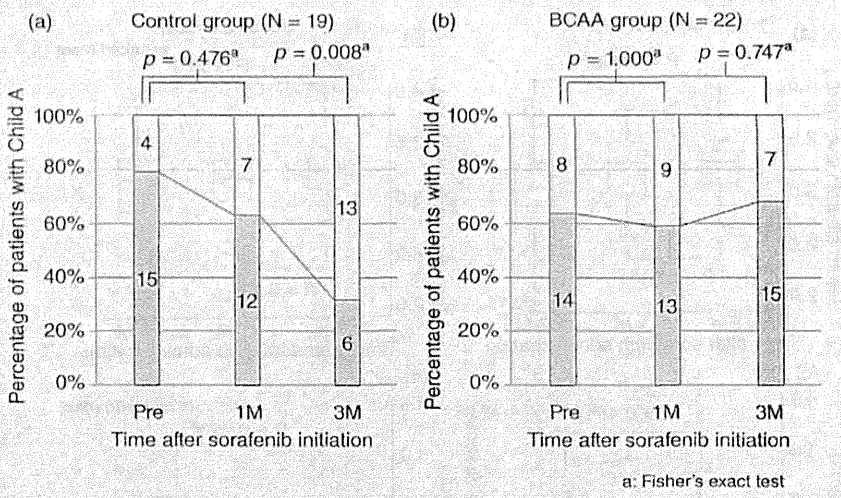

Figure 4 Subgroup analyses of the same population as described in Figure 3. (a,b) Proportion of Child–Pugh classification at the three points, that is, pretreatment, at 1 month and at 3 months in the control group and the branched-chain amino acid (BCAA) group, respectively. (a) The proportion of patients of Child–Pugh A was 78.9%, 63.2% and 31.6%, respectively. At 3 months, the percentage of patients of Child–Pugh A significantly decreased as compared with that in pretreatment status ($P = 0.008$). (b) The proportion of patients of Child–Pugh A was 63.6%, 59.1% and 72.7%, respectively. At 3 months, the percentage of patients of Child–Pugh A did not significantly change as compared with that in pretreatment status ($P = 0.747$). ▭, Child–Pugh A; ▭, Child–Pugh B.

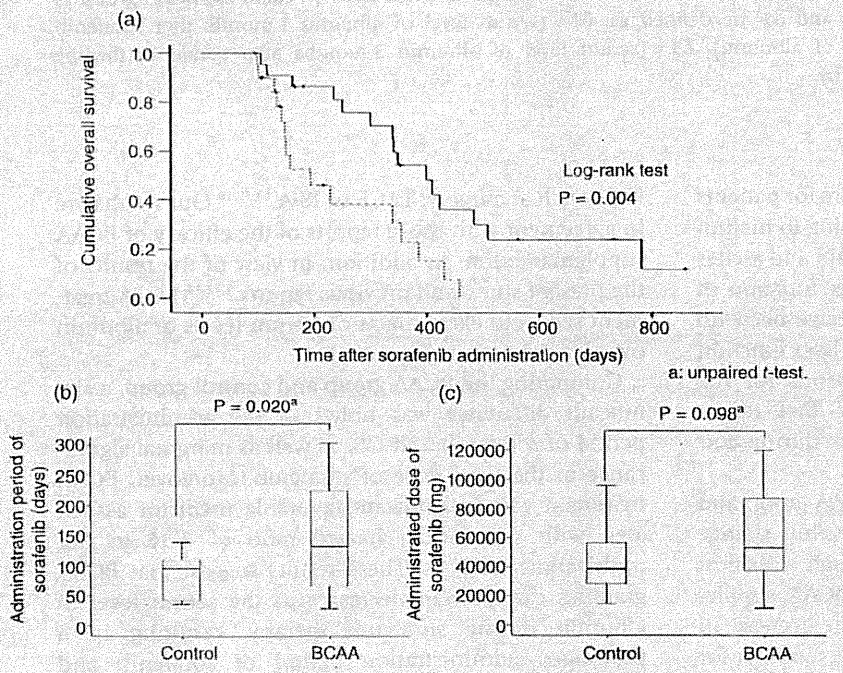

Figure 5 Subgroup analyses of 41 patients who took sorafenib for >1 month with no anticancer therapies other than sorafenib and who could be observed for ≥3 months after sorafenib administration. They involved 22 branched-chain amino acid (BCAA) group patients and 19 control group patients. (a) Cumulative overall survival (OS) in the two groups. The difference in the two groups reached significance ($P = 0.004$). (b) Administration period of sorafenib in the two groups. The difference in the two groups reached significance ($P = 0.020$). (c) Administration dose of sorafenib during the follow-up period in the two groups. Administration dose of sorafenib in the BCAA group tended to be more than that in the control group, but the difference did not reach significance ($P = 0.098$). ——, BCAA ($n = 22$); – – –, control ($n = 19$).

contributing to improving OS. These results are likely to be due to the potential efficacy of BCAA granules, which improve PEM and hypoalbuminemia during sorafenib therapy for HCC patients. Therefore, we strongly recommend that subjects with advanced HCC with a serum level of albumin of 3.5 g/dL or less should be given BCAA granules before and during sorafenib therapy to avoid hypoalbuminemia, and that they should continue sorafenib therapy with an adequate administration period.

Numerous investigators have reported the usefulness of BCAA supplementation in the treatment of LC or HCC with underlying PEM.[7–18] BCAA treatment can correct malnutrition associated with LC in animals and humans, and long-term nutritional supplementation with BCAA also may be useful for the prevention of hepatic failure.[30–32] BCAA supplementation is also effective in downregulating protein metabolism in LC patients by reducing the ammonia (NH_3) level, thus improving the nitrogen balance and resulting in favorable outcomes.[33] It has also been reported that the mechanism underlying these beneficial effects of BCAA may be mediated by stimulation of the activity of hepatocyte growth factor, which induces liver regeneration.[34] Nutritional support may, therefore, have an important role in the management of LC patients with unresectable HCC.[9]

Recently, it was reported that a longer administration period of sorafenib may improve OS in patients with advanced HCC treated with sorafenib.[35] Several investigators have also described patients who achieved a PR (according to RECIST) by administration of sorafenib of long duration.[36] Conversely, liver dysfunction (including hypoalbuminemia) is one of the major reasons for the discontinuance of sorafenib therapy, particularly in Japan. These observations suggest that maintaining liver function reserve is crucial for longer administration of sorafenib and prolonged survival.

There have been several reports about the survival benefit of therapies after sorafenib. Several clinical trials on second-line chemotherapy as post-sorafenib treatment are underway.[37–39] Even if sorafenib therapy is discontinued owing to progressive HCC, anticancer therapies other than sorafenib therapy could help to elicit potential survival benefits.[37–39] To successfully undertake post-sorafenib anticancer therapies, well-maintained liver function after sorafenib therapy is needed. Thus, improving PEM during sorafenib therapy is essential in multidisciplinary therapy for patients with unresectable HCC.

In our analysis, pretreatment serum albumin level was not a significant factor linked to OS, although several studies have showed pretreatment serum albumin level was regarded as one of the significant factors predicting OS in HCC therapy.[20,40] One possible reason for these is that the population of this study is limited to the patients with pretreatment serum level of albumin of 3.5 g/dL or less which reflect poor hepatic functional reserve.

In our multivariate analysis, in addition to BCAA therapy, the Child–Pugh classification, distant metastases and serum levels of DCP were revealed to be significant predictors linked to OS. In the care of HCC patients treated with sorafenib, clinicians should be alert to tumor-related factors and liver function-related factors.

The present study had several limitations. First, this was a retrospective, single-center study. Second, the number of patients in our study was relatively small. Third, the initial dose of sorafenib varied among individual patients, which could have led to bias. Fourth, whether BCAA granules were given to each patient during sorafenib therapy was determined primarily by each attending physician, which also could have led to bias. A larger prospective study is needed to clarify if BCAA granules are useful for preventing hypoalbuminemia during sorafenib therapy and extending OS. However, the results of the present study demonstrate that BCAA granules can prevent the decrease in serum levels of albumin during sorafenib therapy, extend the administration period of sorafenib therapy and prolong OS.

In conclusion, treatment with BCAA during sorafenib therapy in HCC patients is useful for maintaining hepatic functional reserve, which may avoid early discontinuance of sorafenib therapy and result in improvement in OS.

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LIVER CANCER

Clinical features associated with radiological response to sorafenib in unresectable hepatocellular carcinoma: a large multicenter study in Japan

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Keywords
hepatocellular carcinoma – predictive factors – response – sorafenib – survival

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Abstract

Background & Aims: There have been no established predictive factors of responders to sorafenib in patients with unresectable hepatocellular carcinoma (HCC). This study aimed to investigate the factors predicting a good response to sorafenib in Japanese patients with HCC. *Methods:* A total of 465 patients with unresectable HCC in the Japanese Red Cross Liver Study Group were treated with sorafenib between January 2008 and August 2013, and 316 patients with sufficient clinical data were analysed. To determine the factors predicting a good response, the relationships between radiological response and the following clinicopathological factors were analysed: age, gender, performance status, liver function, tumour status and decrease in serum alpha-foetoprotein (AFP) level after 1 month. *Results:* This study included 259 males and 57 females with a median age of 70 years (range, 37–90 years), of which 191 (60.4%) were classified as Barcelona Clinic Liver Cancer stage C, and 271 (85.8%) had Child-Pugh class A liver function. The median overall survival time was 307 days and progression-free survival time was 109 days. According to the modified Response Evaluation Criteria In Solid Tumours, four patients achieved a complete response, 51 achieved a partial response, 136 had stable disease and 125 had progressive disease. Multivariate analysis identified female gender ($P = 0.003$) and decreased serum AFP level after 1 month ($P = 0.042$) as independent predictors of a complete or partial response. *Conclusion:* Our results suggest female gender and a decrease in serum AFP level are independent predictors of good response to sorafenib.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Depending on tumour status and liver function, therapy for HCC may include surgical resection, liver transplantation, transcatheter arterial chemoembolization (TACE), percutaneous radiofrequency ablation, percutaneous ethanol injection and molecular-targeted therapy (MTT). The prognosis of HCC patients who do not undergo radical treatment remains very poor, and HCC is the third most common cause of cancer-related death (1–3).

Although systemic chemotherapy was not shown to be effective for the treatment of advanced HCC for several decades, two randomized studies showed that sorafenib was effective for the treatment of unresectable HCC, and MTT with sorafenib is now approved for use as first-line systemic chemotherapy in these patients (4–6). Although many clinical trials of molecular targeting agents other than sorafenib have been performed, no trials to date have demonstrated that any of these agents have superior efficacy compared with sorafenib for the treatment of unresectable HCC (7–9). Sorafenib is therefore the only agent currently available for the treatment of unresectable HCC in clinical practice. However, only a small proportion of patients achieve a good response to sorafenib. Less than 5% of patients treated with sorafenib in the Sorafenib HCC Assessment

Randomized Protocol (SHARP) trial (4) achieved a partial response (PR) according to the Response Evaluation Criteria In Solid Tumours (RECIST) (10), and we have rarely experienced patients with unresectable HCC who achieved a complete response (CR) to sorafenib therapy (11). Furthermore, sorafenib monotherapy is very expensive, and its cost effectiveness has often been discussed (12, 13). Identification of biomarkers that can predict the response to sorafenib is therefore important. Although several studies have investigated the factors associated with the response to sorafenib (14–23), the factors predicting a favourable response remain unclear. Llovet *et al.* studied the levels of biomarkers including plasma angiopoietin-2 and vascular endothelial growth factor in a subgroup analysis of the SHARP trial, and concluded that none of the biomarkers tested were significant predictors of the response to sorafenib (14). Thus, we conducted this large multicenter study to investigate the factors predicting a good response to sorafenib therapy in patients with unresectable HCC.

Methods

Patients

A total of 465 patients with unresectable HCC in the Japanese Red Cross Liver Study Group were treated with sorafenib between June 2008 and August 2013. Patients received sorafenib therapy according to the inclusion and exclusion criteria demonstrated in SHARP trial (4). Although sorafenib is not generally recommended for patients with Child-Pugh class B or C liver function because of the high risk of serious adverse events, some of these patients with no other effective therapeutic options were given sorafenib according to the decision of their attending physician after a full explanation of the potential risks.

Of the 465 patients, the following were excluded from this study: (i) patients with insufficient pretreatment clinical data (n = 34); (ii) patients who discontinued sorafenib within 1 month (n = 43); and (iii) patients who did not undergo assessment of the therapeutic effectiveness of sorafenib by dynamic CT (n = 41) and serum alpha-foetoprotein (AFP) level at 1–2 months after the initiation of therapy (n = 31). The remaining 316 patients with sufficient available data were analysed in this study (Fig. 1).

Diagnosis of HCC

All patients underwent dynamic CT and/or ultrasonography of the liver before the initiation of sorafenib therapy. A lesion was considered to have typical findings for HCC if dynamic CT showed a blush on the early-phase scan and a defect on the late-phase scan. HCC was also diagnosed by measurement of serum tumour marker levels, including AFP (normal range, <10 ng/ml) and des-gamma-carboxy prothrombin (DCP) (normal range, <40 mAU/ml). Some patients with atypical tumours underwent ultrasound-guided tumour biopsy for histological confirmation of HCC, after giving written informed consent.

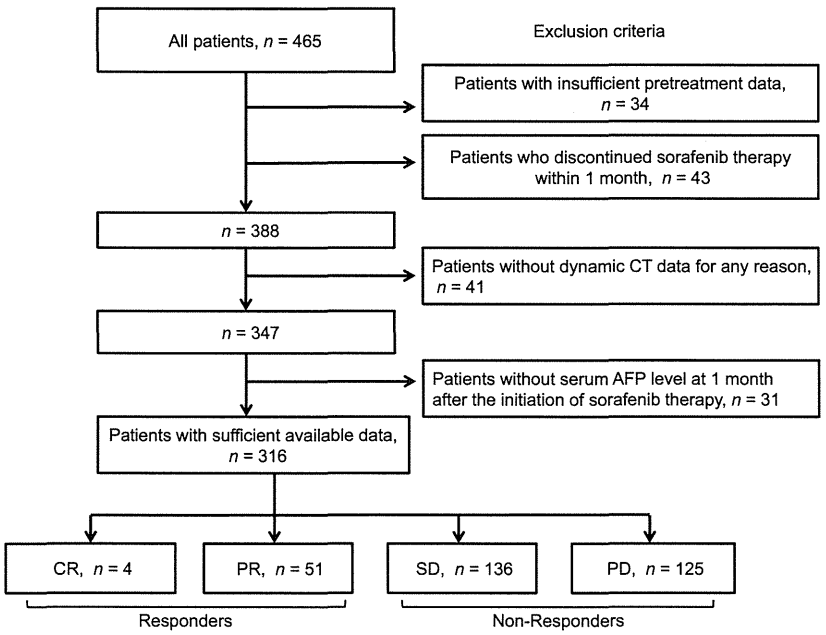

Fig. 1. Flow chart showing the inclusion and exclusion criteria for patient selection. Among 465 patients with HCC treated with sorafenib, 149 were excluded as shown in the chart and the remaining 316 with sufficient available data were included in this study. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Sorafenib therapy

The recommended initial dose of sorafenib for the treatment of HCC is 400 mg twice a day (4–6). The initial dose of sorafenib was determined according to factors such as body weight, BMI, age, comorbid diseases, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (24), and liver function regarding previous reports (25–27). In patients who developed sorafenib-related adverse events, the sorafenib dose was reduced at the discretion of the attending physician. Sorafenib therapy was continued until disease progression, unacceptable drug-related toxicity or the patient's decision to discontinue treatment.

After discontinuing sorafenib, patients potentially able to tolerate other anticancer therapies received systemic chemotherapy, TACE or transcatheter arterial infusion chemotherapy depending on their ECOG-PS, tumour status and liver function. Some patients entered ongoing clinical trials of second-line chemotherapy.

Study protocol

This study retrospectively analysed patient records at each participating hospital. This study protocol was approved by the ethics committee of each hospital. Written informed consent was obtained from each patient prior to sorafenib therapy. This study protocol complied with all provisions of the Declaration of Helsinki.

The radiological data were collected for all patients, and the objective response rate (ORR) for all patients was calculated. The response to sorafenib was evaluated every 4–8 weeks using the modified RECIST (mRECIST) (28) and/or tumour marker levels. ORR was defined as the percentage of analysed patients who achieved a CR or PR according to mRECIST. The relationships between the radiological response and the following clinicopathological factors were examined: age, gender, body weight, ECOG-PS, antitumour therapies prior to sorafenib such as surgery or TACE, results of blood test including aspartate aminotransferase level, alanine aminotransferase level, alkaline phosphatase level, gamma-glutamyl transpeptidase (γGTP) level, lactate dehydrogenase (LDH) level, haemoglobin level, platelet count, albumin level, total bilirubin level and cholinesterase level, ascites, tumour factors including portal vein invasion, tumour burden, lung metastasis, bone metastasis, serum tumour marker levels, and a >20% decrease in the serum AFP level at 1 month after the initiation of sorafenib therapy. All ultrasound-guided tumour biopsy specimens were stained with haematoxylin and eosin, and the degree of differentiation was determined by a single pathologist at each hospital according to Edmondson's classification (29). The relationship between the degree of tumour differentiation and the radiological response to sorafenib therapy was analysed.

Statistical analysis

Categorical variables were analysed using Chi-square test and Fisher's exact test. Continuous variables were analysed using the unpaired *t* test, if appropriate. Overall survival (OS) curves were generated using the Kaplan–Meier method and compared using the log-rank test. OS was calculated from the initiation of sorafenib therapy until death from any cause or the last follow-up. Progression-free survival (PFS) was calculated from the initiation of sorafenib therapy until the diagnosis of disease progression or death from any cause. Factors predicting a response to therapy were identified by multivariate logistic regression analysis, including all factors with $P < 0.2$ on univariate analyses. Data were analysed using SPSS (version 21.0; SPSS, Chicago, IL, USA). Two-tailed *P* values of <0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of all 465 patients and of the 316 analysed patients with sufficient available data are shown in Table 1. This study population included 259 males and 57 females with a median age of 70 years (range, 37–90 years). Of these, 191 patients (60.4%) were classified as BCLC stage C and 119 (37.7%) as BCLC stage B. Fifty patients had hepatitis B virus infection, 178 had hepatitis C virus infection, two had both hepatitis B and C virus infection, and the remaining 86 did not have hepatitis virus infection. The background liver diseases included autoimmune hepatitis, alcoholic cirrhosis, and non-alcoholic steatohepatitis. Liver function was Child-Pugh class A in 271 patients (85.8%) and Child-Pugh class B in 43 (13.6%). Most patients had received previous therapy for HCC, including one or more sessions of TACE, percutaneous radiofrequency ablation or percutaneous ethanol injection, and surgery (Table 1).

The median duration of sorafenib therapy was 133 days (range, 28–1211 days). The reason for discontinuation of therapy was disease progression in about half of the cases and adverse events including drug-related side effects in the other half.

Treatment response

According to mRECIST, four patients achieved a CR, 51 achieved a PR, 136 had stable disease (SD) and 125 had progressive disease (PD). The ORR (proportion who achieved PR or CR) was 17.4% (55/316), and the disease control rate (DCR; proportion who achieved CR, PR or SD) was 60.4% (191/316).

OS, PFS and causes of death

The Kaplan–Meier curves for OS and PFS are shown in Fig. 2. The median OS time was 307 days and the

Table 1. Baseline characteristics of patients

Variable		All patients (n = 465)	Analysed patients (n = 316)	P
Age (years)		71 (37–90)	70 (37–90)	0.877*
Gender	Male/Female	376/89	259/57	0.386†
Body weight (kg)		58.4 (30–110)	57.5 (30–110)	0.580*
Body mass index (kg/m^2)		22.5 (13.7–42.2)	22.7 (13.7–42.2)	0.887*
Aetiology of liver disease	Hepatitis B	70	50	0.998†
	Hepatitis C	267	178	
	No hepatitis B/C	123	86	
	Hepatitis B and C	5	2	
BCLC stage	A/B/C/D	4/163/295/3	4/119/191/2	0.801†
Tumour invasion into portal vein	Present/Absent	110/355	69/247	0.603†
ECOG-PS	0/1/2	350/101/14	251/60/5	0.280†
Child-Pugh classification	A/B/C	377/85/3	271/43/2	0.253†
Pretreatment AFP level (ng/ml)		137.5 (1.9–1 460 000)	149 (1.7–270 300)	0.192*
Pretreatment DCP level (mAU/ml)		651 (9–1 685 300)	524 (9–847 000)	0.268*
Previous therapies for HCC				
TACE	yes/no	391/74	276/40	0.217†
RFA or PEI	yes/no	232/233	165/151	0.560†
Surgery	yes/no	92/373	65/251	0.786†

*Unpaired t test.

†Fisher's exact test.

Data are the number or median (range).

AFP, alpha-foetoprotein; BCLC, Barcelona Clinic Liver Cancer; DCP, des-gamma-carboxy prothrombin; ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; RFA, radiofrequency thermal ablation; TACE, transcatheter arterial chemoembolization.

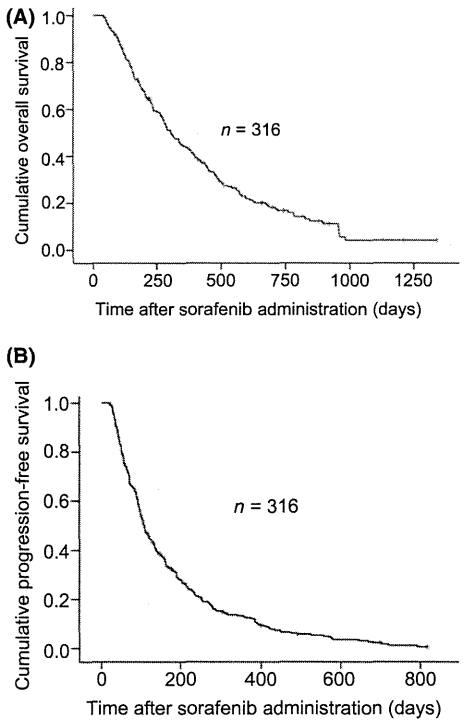

Fig. 2. Kaplan–Meier curves for (A) overall survival (OS) and (B) progression-free survival (PFS) of the patients included in this study (n = 316). The median OS time was 307 days and the median PFS time was 109 days.

1- and 3-year OS rates were 45% and 5% respectively. The median PFS time of all analysed patients was 109 days. The mean observation period was 315 days. A total of 223 deaths and 291 cases of disease progression were observed during the observation period. The cause of death was HCC-related in 78% of cases (179/229). The other causes of death were liver failure (26 cases), other conditions such as pneumonia (12 cases), and unknown (12 cases).

Complete response in four patients

Four patients in this study achieved a CR according to mRECIST. The clinical characteristics of these four patients are shown in Table 2. Three patients had multiple intrahepatic nodules, and achieved complete disappearance of intratumoural vascularity after sorafenib therapy. The other patient (Case 4) had multiple lung metastases, all of which completely disappeared after 4 months of sorafenib therapy. It took longer than 2 months for the serum AFP level to normalize in three patients. All four patients achieved long-term survival.

Predictive factors for a good response to sorafenib therapy

Univariate analyses showed that female gender, lower DCP level, normal LDH level and >20% decrease in AFP level were significantly associated with higher ORR (P = 0.003, 0.018, 0.048 and 0.029, respectively), and that a pretreatment total bilirubin level <1.0 mg/dl and γGTP level <80 IU/L tended to be associated with

Table 2. Characteristics of HCC patients who achieved a CR

	Case 1	Case 2	Case 3	Case 4
Age/Gender	79/male	81/female	45/female	77/female
Aetiology	HCV	No HBV or HCV	HBV	HCV
ECOG-PS	0	0	0	0
Pretreatment Child-Pugh score	5	5	5	6
BCLC stage	B	B	B	C
Previous therapies	TACE, RFA	TACE, RFA	TACE, RFA	TACE, RFA, surgery
Reason for introduction of sorafenib	Refractory to TACE	Refractory to TACE	Refractory to TACE	Lung metastases
Initial dose of sorafenib (mg/day)	400	400	400	400
Duration of sorafenib therapy (day)	962	526	272	95
Reason for discontinuation of sorafenib	Continued	Progressive disease	Continued	Liver damage
Serum AFP level (pretreatment/minimum)	8.8/3.9	114/8	370/9.4	6952/6.3
Time to normalization of serum AFP level(day)	–	90	76	120
Major radiological change in CT scan	Complete disappearance of intratumoural vascularity	Complete disappearance of intratumoural vascularity	Complete disappearance of intratumoural vascularity	Disappearance of all lung metastases
Observation period (day), alive or dead	962, alive	621, dead	541, alive	1128, alive

AFP, alpha-foetoprotein; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; CT, computed tomography; ECOG-PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RFA, radiofrequency thermal ablation; TACE, transcatheter arterial chemoembolization.

higher ORR ($P = 0.071$ and 0.054, respectively) (Fig. 3; Table 3). The ORR was 14.3% (37/259) for males and 31.6% (18/57) for females ($P = 0.003$) (Fig. 3A).

Multivariate analysis including the eight factors with $P < 0.2$ on univariate analyses identified female gender [odds ratio (OR), 2.876; 95% confidence interval (CI), 1.350–6.123; $P = 0.001$] and a >20% decrease in AFP level (OR, 1.982; 95% CI, 1.026–3.829; $P = 0.042$) as independent predictors of higher ORR. The P values, ORs, and 95% CIs for the other five factors with $P < 0.1$ on univariate analyses are shown in Table 3.

Clinical characteristics according to gender

Multivariate analysis showed that female gender was a significant predictor of ORR. We therefore further analysed our data according to gender (Table 4). Females were significantly older and weighed significantly less than males. Females also tended to have a worse ECOG-PS and lower initial dose of sorafenib than males. There were no significant differences in pretreatment blood test results between males and females. Analysis of adverse events showed that the rate of hand-foot syndrome, which is a major sorafenib-related adverse event, was not significantly different between males and females [55.6% (144/259) vs. 57.9% (33/57), $P = 0.770$]. The median duration of sorafenib therapy was almost the same in males and females (132 days vs. 147 days, $P = 0.961$). OS and PFS were not significantly different between males and females ($P = 0.227$ and 0.887 respectively) (Fig. 4).

Degree of tumour differentiation

Sixty-two biopsy specimens were obtained from 62 patients before the initiation of sorafenib therapy. Histological examination showed that 25 cases were Edmondson grade I (Ed. I), 23 were Ed. II and 14 were Ed. III. The number of patients with best tumour response of CR/PR/SD/PD was 1/6/13/5 in Ed I, 0/4/7/12 in Ed. II and 0/2/4/8 in Ed. III respectively. The DCR was significantly higher in patients with Ed. I disease than in other patients [80.0% (20/25) vs. 45.9% (17/37), $P = 0.009$]. In this small subgroup, no other factors showed a significant association with disease control on univariate analyses, and multivariate analysis was therefore not performed. There was no significant association between the degree of tumour differentiation and ORR.

Tumour response according to the initial dose of sorafenib

The initial dose of sorafenib was reduced in 186 patients (55.9%) for the reasons described above (reduced-dose group), to 600 mg per day in two patients, 400 mg per day in 173 patients, and 200 mg per day in 11 patients. In this reduced-dose group, CR was achieved in four patients, PR in 28, SD in 75 and PD in 79. In patients who received an initial dose of 800 mg/day, CR was achieved in 0, PR in 23, SD in 57 and PD in 50. The ORR and DCR were almost the same in these two groups [ORR: 17.2% (32/186) vs. 17.7% (23/130), $P = 0.999$; DCR: 57.5% (107/186) vs. 61.5% (80/130), $P = 0.765$].

Subgroup analyses according to BCLC stage and child-pugh class

We performed subgroup analyses according to BCLC stage. ORR and DCR of BCLC-B patients was 15% (22/119) and 69% (83/119), and only female gender was