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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Study

Prolonged survival in patients with hand-foot skin reaction secondary to cooperative sorafenib treatment

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Abstract

BACKGROUND
Sorafenib is an oral drug that prolongs overall survival (OS) in patients with hepatocellular carcinoma. Adverse events, including hand-foot skin reaction (HFSR), lead to permanent sorafenib discontinuation.

AIM
To clarify the association between interventions for adverse events and patient prognosis.

METHODS
We performed a retrospective, multicenter study of patients treated with sorafenib monotherapy between May 2009 and March 2018. We developed a mutual cooperation system that was initiated at the start of sorafenib treatment to effectively manage adverse events. The mutual cooperation system entailed patients receiving consultations during which pharmacists provided accurate information about sorafenib to alleviate the fear and anxiety related to adverse events. We stratified the patients into three groups: Group A, patients without HFSR but with pharmacist intervention; Group B, patients with HFSR and pharmacist interventions unreported to oncologists (nonmutual cooperation system); and Group C, patients with HFSR and pharmacist interventions known to oncologists (mutual cooperation system). OS and time to treatment failure (TTF) were evaluated using the Kaplan-Meier method.

RESULTS
We enrolled 134 patients (Group A, *n* = 41; Group B, *n* = 30; Group C, *n* = 63). The

median OS was significantly different between Groups A and C (6.2 *vs* 13.9 mo, p < 0.01) but not between Groups A and B (6.2 *vs* 7.7 mo, *P* = 0.62). Group A *vs* Group C was an independent OS predictor (HR, 0.41; 95%CI: 0.25-0.66; *P* < 0.01). In Group B alone, TTF was significantly lower and the nonadherence rate was higher (*P* < 0.01). In addition, the Spearman's rank correlation coefficients between OS and TTF in each group were 0.41 (Group A; *P* < 0.01), 0.13 (Group B; *P* = 0.51), and 0.58 (Group C; *P* < 0.01). There was a highly significant correlation between OS and TTF in Group C. However, there was no correlation between OS and TTF in Group B.

CONCLUSION

The mutual cooperation system increased treatment duration and improved prognosis in patients with HFSR. Future prospective studies (*e.g.*, randomized controlled trials) and improved adherence could help prevent OS underestimation.

Key Words: Hepatocellular carcinoma; Sorafenib; Pharmacists; Oncologists; Prognosis; Duration of therapy

Core Tip: We investigated the effect of cooperation between oncologists and pharmacists (mutual cooperation system) on the prognosis of patients with advanced hepatocellular carcinoma treated with sorafenib and found that cooperation increased medication adherence. Prolonged adherence was correlated with overall survival and time to treatment failure in patients with sorafenib-related hand-foot skin reactions. Our mutual cooperation system could be used to manage patients treated with various multikinase inhibitors and improve overall survival in studies that use sorafenib as the control drug. Future clinical investigations that include measures to improve medication adherence could eliminate the underestimation of medication efficacy that may otherwise occur due to preventable nonadherence.

INTRODUCTION

Sorafenib is a multikinase inhibitor used to treat advanced hepatocellular carcinoma (HCC)[1,2]. Although sorafenib prolongs overall survival (OS) in patients with HCC, it is associated with various adverse events (AEs) that may lead to permanent discontinuation[3].

Previous studies found that hand-foot skin reaction (HFSR) was a prognostic marker of longer survival[4-6]. While HFSR is an important predictor of survival outcomes in clinical practice and clinical sorafenib trials, AE management could influence the efficacy of HFSR as a prognostic factor. A recent study showed that increased clinician experience with AEs reduced the potential for discontinuing sorafenib therapy, resulting in a longer OS in patients with HCC[7]. Nevertheless, it takes a long time for clinicians to develop the necessary experience for the management of AEs, and even with experience, it takes a substantial amount of time to provide a system of adequate follow-up after sorafenib initiation.

As sorafenib is administered orally, its successful use for HCC treatment relies on patient medication adherence. However, many studies indicate that patients with cancer are sometimes nonadherent when prescribed oral drugs[8,9], and AEs are the main cause of poor adherence[10]. Poor adherence can lead to poor outcomes, and clinicians may wrongly conclude that a drug is ineffective because the response to treatment is insufficient[11].

It is important for patients to actively participate in making treatment decisions and then receive treatment according to their decisions to improve adherence[12]. We introduced behavior change techniques (patient education, medication regimen management, pharmacist-led interventions)[13,14] in our facilities as interventions to promote adherence. Using a preliminary simulation, we estimated that collecting patient information takes at least 20 min. From this, we concluded that it is difficult for oncologists to manage drugs that cause various AEs (*e.g.*, sorafenib) without assistance due to their obligations to many patients. Thus, we developed a mutual cooperation system involving collaboration between oncologists and pharmacists to ensure effective AE management. This mutual cooperation system consisted of the initial intervention by a pharmacist followed by a medical examination by an oncologist. However, this system was affected by the patient's behavior because patients were not obliged to follow the system. Some patients received intervention from a pharmacist after a medical examination by an oncologist.

Effective AE management that improves medication adherence has a considerable impact on survival outcomes. Previous single-center studies suggest that healthcare provider interventions improve adherence, and the onset of HFSR was a favorable prognostic factor of OS in patients with HCC[15,16]. However, little is known about the association between prognosis and medication adherence in patients with HCC, and multicenter studies on this relationship are lacking. Therefore, we aimed to compare the impact of different AE interventions on patient prognosis.

MATERIALS AND METHODS

Study design

We retrospectively evaluated patients with advanced HCC treated with sorafenib monotherapy and no subsequent chemotherapeutic agent between May 2009 and March 2018 using the medical records of the following core hospitals in Japan: Hitachi General Hospital, Ibaraki Prefectural Central Hospital, Ibaraki Cancer Center, and Tokyo Medical University Ibaraki Medical Center. These hospitals are core hospitals that were designated by the government to provide specialized cancer medical care. The patients were separated into three groups: Group A, patients without HFSR but with pharmacist intervention (this intervention was performed by pharmacists who did not share interview information with the oncologist; it is called nonmutual cooperation system); Group B, patients with HFSR and nonmutual cooperation system; and Group C, patients with HFSR and intervention by pharmacists who shared interview information with the oncologist (mutual cooperation system).

Patient selection

We included patients with stage B or C HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system. The indication criteria for sorafenib administration were as follows: Child-Pugh grade A or B; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; alanine aminotransferase < 5-fold the upper limit of the normal range; total bilirubin level < 2.0 mg/dL; neutrophil count > 1500/μL; hemoglobin level ≥ 8.5 g/dL; platelet count > 75000/μL; and no dialysis requirement. The study exclusion criteria were as follows: Patients with a history of thrombosis or ischemic heart disease, pregnant women and those who could become pregnant, and patients with brain metastases. Our study protocol was approved by the ethics committee of each hospital and was performed according to the ethical guidelines of the 1975 Declaration of Helsinki. We obtained informed consent using an opt-out option on each facility's website (see Institution website uniform resource locators). This study was registered with the University Hospital Medical Information Network (UMIN) (ID: UMIN000038701).

Data collection

We collected patient data from the start of sorafenib, including age, sex, etiology of underlying liver disease, Child-Pugh score, history of present illness, medical history, tumor marker level [alpha-fetoprotein (AFP)], ECOG performance status, and relevant laboratory tests, including total bilirubin, albumin, and international normalized ratio (INR). Laboratory tests and tumor marker levels were obtained every 8–10 wk until permanent sorafenib discontinuation.

Computed tomography evaluations

Sorafenib response evaluations on computed tomography (CT) were scheduled for 8 wk after the first treatment, and subsequent evaluations were planned every 8 wk. Thoracic, abdominal, and pelvic CT scans were performed with intravenous iodinated contrast media. CT evaluations were conducted based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[17] by an oncologist.

Intervention

Pharmacists with special expertise provided medical care at the pharmacist's outpatient clinic before or after a patient was medically examined by an oncologist. Every 8 wk at each visit, an AE evaluation, a residual drug count, self-management advice, and patient education, including descriptions of successful cases of AE management, pharmacist support, and advice for relieving patient anxiety and misunderstanding, were conducted. AEs were evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0. Pharmacists recommended that all patients use heparinoids before sorafenib treatment to prevent AEs. Additionally, the prophylactic use of urea cream to prevent dermatologic AEs was recommended after beginning sorafenib treatment. Pharmacist intervention began at the start of sorafenib treatment and continued until treatment ended.

Mutual cooperation system

We developed a mutual cooperation system that was initiated at the start of sorafenib treatment to manage AEs effectively. Although patients in Groups B and C received medical advice from oncologists and pharmacists, the systems differed. Group C received 20- to 30-min consultations during which pharmacists provided accurate information about sorafenib to alleviate fear and anxiety related to AEs. After each visit, the pharmacist summarized the consultation results in a report and discussed their findings with an oncologist. Group B patients received a 5- to 10-min session during which pharmacists provided the same information about sorafenib that Group C had received. These pharmacist consultations were brief because a thorough medical examination by an oncologist had already been completed. Furthermore, the pharmacist did not record the consultation content in the medical chart because the visit involved verbal intervention only, and a detailed report was unnecessary.

Sorafenib therapy and AE management

Sorafenib was administered at a dose of 400 or 800 mg/d. The initial dose of sorafenib was determined by an oncologist. At the start of sorafenib treatment, all patients received information about AEs from a pharmacist and an oncologist. Patients who developed an AE could confer with their consulting pharmacist or prescribing oncologist. Pharmacists collected and recorded patient data, including the AE grade (according to NCI-CTCAE version 5.0), AE time of onset, and emotional response of the patient to the AE. Oncologists performed dose modifications throughout treatment, including reductions, interruptions, and reintroductions, according to the drug manufacturer's package insert for sorafenib.

Criteria for permanent sorafenib discontinuation

Sorafenib was permanently discontinued when any of the following events occurred: (1) Tumor progression, defined as either radiologic (by the mRECIST criteria) or clinically progressive disease (*e.g.*, ECOG performance status decline or onset of severe symptoms with no connection to liver failure); (2) Unacceptable AEs, defined as moderate to severe AEs (*e.g.*, grades 2–4) that persisted after dose reduction or temporary treatment interruption; or (3) Liver decompensation, defined as gastrointestinal bleeding, ascites, jaundice, or encephalopathy[3]. All patients were managed by an oncologist and received excellent supportive care after sorafenib was permanently discontinued. Time to treatment failure (TTF) was defined as the duration from the start of sorafenib treatment to permanent discontinuation. The proportion of days covered (PDC) was defined as the TTF divided by the time to radiologic progressive disease after sorafenib[18]. Nonadherence was defined as a PDC of ≤ 80%[19].

Statistical analysis

Categorical variables were assessed using the chi-square test and are presented as frequencies or percentages. Continuous variables were analyzed using the Mann-Whitney *U* test and are expressed as the mean ± SD. OS and TTF were evaluated using the Kaplan-Meier method. A landmark analysis[20] was performed to consider HFSR cases that might have occurred if a patient with HCC had not died as a guarantee-time

bias. The analysis was performed using the time when the highest-grade HFSR occurred in 50% or more of the patients as a landmark (here, 30 d). The log-rank test was used to estimate differences in survival curves. Additionally, we used Cox regression analyses to evaluate the relationship between the time to the occurrence of an event and explanatory variables. Logistic regression analyses were used to evaluate the relationship between nonadherence and explanatory variables.

We included the following baseline characteristics as variables in our univariate analysis: age, sex, etiology of liver disease, bilirubin level, albumin level, INR, BCLC stage, ECOG performance status, macrovascular invasion, extrahepatic spread, serum AFP level, and number of previous transarterial chemoembolization (TACE) procedures for liver cancer. Variables identified as significant in the univariate analysis were included in the multivariate analysis. The correlations between OS and TTF were assessed by Spearman's rank correlation coefficient. A p-value less than 0.05 was considered statistically significant. We used the Bonferroni correction for multiple comparisons to adjust the familywise error rate when comparing differences between the three groups. The statistical methods of this study were reviewed by Kamoshida T from the Department of Gastroenterology, Hitachi General Hospital, Japan. All statistical analyses were performed using SPSS software, version 22 (IBM Corp., Armonk, NY, United States).

RESULTS

Patients
We included 134 patients [median age, 69 years (range, 41–89 years); male, *n* = 99; female, *n* = 35] with advanced HCC who received sorafenib monotherapy without posttreatment (Group A, *n* = 41; Group B, *n* = 30; Group C, *n* = 63). The main etiological factor was hepatitis C virus (HCV) (77/134 patients, 57.5%), followed by hepatitis B virus (HBV) (30/134 patients, 22.4%).

Baseline characteristics
All patients had cirrhosis [Child-Pugh A, *n* = 117 (87.3%); Child-Pugh B, *n* = 17 (12.7%)]. HCC was BCLC stage B in 55 patients (41.0%) and BCLC stage C in 79 patients (59.0%). None of the patients had a second primary cancer. Portal vein thrombosis was present in 35 patients (26.1%), and extrahepatic metastases were found in 67 patients (50.0%) (Table 1).

AEs
An AE of at least grade 1 was observed in all patients after sorafenib administration. However, none of the patients experienced any grade 4 AEs. The main AEs in all groups were fatigue (30.6%), diarrhea (39.6%), hypertension (31.3%), anorexia (29.9%), and thrombocytopenia (38.8%) (Table 2). Many patients required temporary sorafenib interruption because of AEs (Group A, 19.5%; Group B, 6.7%; Group C, 41.3%). Of patients who temporarily stopped taking sorafenib, the rate of those who resumed treatment at a reduced dose was the highest in Group C (Group A *vs* Group B, *P* = 0.70; Group A *vs* Group C, *P* = 0.11; Group B *vs* Group C, *P* < 0.01) (Table 3).

Radiological response evaluations
CT examinations performed every 2 mo showed that the disease control rate (DCR) gradually decreased in all groups. The response rate (RR) and DCR 8 mo after the start of sorafenib treatment were the highest in Group C (RR, 9.5%; DCR, 65.1%) (Table 4).

Permanent sorafenib discontinuation
The main causes of permanent drug discontinuation were HCC progression and sorafenib-related AE intolerance. Permanent discontinuation due to AE intolerance occurred most frequently in Group B (Group A (17.1%) *vs* Group B (60.0%), *P* < 0.01; Group A (17.1%) *vs* Group C (20.6%), *P* = 1.00; Group B (60.0%) *vs* Group C (20.6%), *P* < 0.05) (Table 5).

OS after sorafenib therapy
The median OS was 6.2 mo in Group A, 7.7 mo in Group B, and 13.9 mo in Group C. The difference in the median OS was significant between Groups A and C (*P* < 0.01). In multivariate analysis, Group A *vs* Group C (HR, 0.41; 95%CI: 0.25–0.66; *P* < 0.01) and BCLC-B (HR, 0.60, 95%CI: 0.41–0.89; *P* = 0.01) were independent predictors of survival

Table 1 Baseline characteristics of patients in Groups A, B, and C				
	Group A (*n* = 41)	Group B (*n* = 30)	Group C (*n* = 63)	*P* value
Age (yr)	70 (43–89)	67 (41–87)	69 (48–87)	0.233
Sex				
Male, *n* (%)	33 (80.5)	22 (73.3)	44 (69.8)	0.481
Child-Pugh class, *n* (%)				0.288
A	33 (80.5)	27 (90.0)	57 (90.5)	
B	8 (19.5)	3 (10.0)	6 (9.5)	
Etiology, *n* (%)				
HCV	22 (53.7)	11 (36.7)	44 (69.8)	0.235
HBV	9 (21.9)	10 (33.3)	11 (17.5)	0.417
Other	10 (24.4)	9 (30.0)	8 (12.7)	0.109
Portal vein thrombosis	14 (34.1)	10 (33.3)	11 (17.5)	0.099
Extrahepatic spread, *n* (%)	20 (48.8)	19 (63.3)	28 (44.4)	0.230
AFP (ng/mL), *n* (%)				
> 400	17 (41.5)	17 (56.7)	29 (46.0)	0.437
BCLC staging, *n* (%)				0.333
Stage B	15 (36.6)	10 (33.3)	30 (47.6)	
Stage C	26 (63.4)	20 (66.7%)	33 (52.4)	
ECOG performance status, *n* (%)				0.955
0	30 (75.6)	22 (73.3)	46 (73.0)	
1	10 (24.4)	8 (26.7)	17 (27.0)	
Total bilirubin (mg/dL)	0.99 ± 0.36	0.91 ± 0.37	0.83 ± 0.33	0.052
Albumin (g/L)	3.61 ± 0.50	3.73 ± 0.54	3.82 ± 0.49	0.301
INR	1.14 ± 0.11	1.15 ± 0.16	1.14 ± 0.19	0.481
Pre-sorafenib TACE procedures, *n* (%)				0.531
0	13 (31.7)	9 (30.0)	20 (31.8)	
1	3 (7.3)	6 (20.0)	13 (20.6)	
2	6 (14.6)	1 (3.3)	4 (6.4)	
3	4 (9.8)	2 (6.7)	8 (12.7)	
4	5 (12.2)	3 (10.0)	12 (19.0)	
> 5	10 (24.4)	9 (30.0)	6 (9.5)	

AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; HCV: Hepatitis C virus; HBV: Hepatitis B virus; INR: International normalized ratio; TACE: Transcatheter arterial chemoembolization; ECOG: Eastern Cooperative Oncology Group.

(Figures 1 and 2, Table 6).

Mutual cooperation system evaluation
The median TTF in Group C was 5.0 mo (95%CI: 3.8–6.5), which was the highest of all the groups [Group C (5.0 mo) *vs* Group A (2.1 mo), *P* < 0.01; Group C (5.0 mo) *vs* Group B (0.5 mo), *P* < 0.01]. In multivariable Cox regression analysis, Group A *vs* Group B (HR, 1.69, 95%CI, 1.04–2.75; *P* = 0.03) and Group A *vs* Group C (HR, 0.53; 95%CI: 0.35–0.81; *P* < 0.01) were significant predictors of TTF (Table 7). The proportions of patients with a PDC of < 0.8 were 29.3% in Group A, 73.3% in Group B, and 23.8% in Group C. Group B had a significantly higher sorafenib PDC than Groups A (*P* < 0.01) and C (*P* < 0.01). Adjusted logistic regression analysis showed that nonadherence (PDC ≤ 0.8) was associated with Group B *vs* Group A (OR, 0.11; 95%CI:

Table 2 Prevalence of adverse events after beginning sorafenib, according to CTCAE version 5.0, *n* (%)

	Group A (*n* = 41)				Group B (*n* = 30)				Group C (*n* = 63)			
	All grades	Grade 1	Grade 2	Grade 3	All grades	Grade 1	Grade 2	Grade 3	All grades	Grade 1	Grade 2	Grade 3
Any adverse event	37 (90.2)	30 (73.2)	18 (43.9)	5 (12.2)	30 (100)	28 (93.3)	24 (80.0)	14 (46.6)	63 (100)	58 (92.1)	36 (57.1)	14 (22.2)
Hand-foot skin reaction	0 (0)	0 (0)	0 (0)	0 (0)	30 (100)	15 (50.0)	10 (33.3)	5 (16.7)	63 (100)	39 (61.9)	19 (30.2)	5 (7.9)
Anemia	17 (41.5)	8 (19.5)	8 (19.5)	1 (2.4)	20 (66.6)	13 (43.3)	4 (13.3)	3 (10.0)	23 (36.5)	14 (22.2)	7 (11.1)	2 (3.2)
Diarrhea	15 (36.6)	12 (29.3)	3 (7.3)	0 (0)	11 (36.6)	9 (30.0)	1 (3.3)	1 (3.3)	27 (42.8)	21 (33.3)	2 (3.2)	4 (6.3)
Fatigue	14 (34.1)	10 (26.8)	3 (7.3)	0 (0)	11 (36.6)	7 (23.3)	4 (13.3)	0 (0)	16 (25.4)	10 (15.9)	6 (9.5)	0 (0)
Anorexia	14 (34.1)	10 (24.4)	3 (7.3)	1 (2.4)	7 (23.3)	5 (16.7)	1 (3.3)	1 (3.3)	19 (30.1)	15 (23.8)	4 (6.3)	0 (0)
Hypertension	12 (29.3)	10 (24.4)	2 (4.9)	0 (0)	7 (23.3)	2 (6.6)	5 (16.7)	0 (0)	23 (36.5)	16 (25.4)	4 (6.3)	3 (4.8)
Thrombocytopenia	9 (22.0)	2 (4.9)	4 (9.7)	3 (7.3)	23 (76.7)	10 (33.3)	8 (26.7)	5 (16.7)	20 (31.7)	10 (15.9)	5 (7.9)	5 (7.9)
Alopecia	6 (14.6)	4 (9.7)	2 (4.9)	0 (0)	2 (6.6)	2 (6.6)	0 (0)	0 (0)	20 (31.7)	19 (30.2)	1 (1.6)	0 (0)
Hepatic encephalopathy	1 (2.4)	0 (0)	1 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 3 Dose modification related to adverse events

	Group A (*n* = 41)	Group B (*n* = 30)	Group C (*n* = 63)	Group A *vs* Group B, *P* value	Group A *vs* Group C, *P* value	Group B *vs* Group C, *P* value
Dose reduction to initial dose of sorafenib	8/41 (19.5%)	2/30 (6.7%)	26/63 (41.3%)	0.700	0.108	0.005
Re-escalation to initial dose of sorafenib	2/8 (25.0%)	2/2 (100.0%)	2/26 (7.7%)	NA	NA	NA

NA: Not available.

Table 4 Radiological response according to the modified response evaluation criteria in solid tumors

	Group A (*n* = 41)	Group B (*n* = 30)	Group C (*n* = 63)
Complete response	0	1	1
Partial response	1	1	5
Stable disease	10	11	35
Progressive disease	30	17	22
Response rate	2.4%	6.7%	9.5%
Disease control rate	26.8%	43.3%	65.1%

0.04–0.36; *P* < 0.01) and Group B *vs* Group C (OR, 0.09; 95%CI: 0.03–0.27; *P* < 0.01) (Figure 3, Table 8).

Correlation between OS and TTF
The Spearman's rank correlation coefficients between OS and TTF in each group were 0.41 (Group A; *P* < 0.01), 0.13 (Group B; *P* = 0.51), and 0.58 (Group C; *P* <0.01). There was a highly significant correlation between OS and TTF in Group C. However, there was no correlation between OS and TTF in Group B.

Table 5 Reasons for permanent sorafenib discontinuation, *n* **(%)**

	Group A (*n* = 41)	Group B (*n* = 30)	Group C (*n* = 63)	Group A *vs* Group B, *P* value	Group A *vs* Group C, *P* value	Group B *vs* Group C, *P* value
Progression	26 (63.4)	7 (23.3)	33 (52.4)	0.006	1.000	0.046
Intolerance	7 (17.1)	18 (60.0)	13 (20.6)	0.002	1.000	0.001
Liver failure	6 (14.6)	3 (10.0)	8 (12.7)	1.000	1.000	1.000
Other	2 (4.9)	2 (6.7)	9 (14.3)	1.000	0.690	1.000

Table 6 Prognostic factors of overall survival by multivariable Cox regression analysis

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (within 70 yr)	0.867	0.603–1.246	0.440	-	-	-
Male	1.216	0.802–1.842	0.357	-	-	-
Etiology (HBV)	1.313	0.809–2.133	0.271	-	-	
BCLC stage B	0.667	0.459–0.969	0.033	0.601	0.405–0.891	0.011
Portal vein thrombosis	1.677	1.092–2.575	0.018	1.133	0.674–1.903	0.638
Extrahepatic spread	0.740	0.509–1.074	0.113	0.671	0.419–1.076	0.098
AFP (> 400 ng/mL)	1.282	0.893–1.839	0.178	1.370	0.936–2.006	0.105
ECOG Performance status 1	0.752	0.488–1.158	0.196	1.042	0.636–1.708	0.869
Group A *vs* Group B	0.703	0.431–1.147	0.159	0.658	0.398–1.088	0.103
Group A *vs* Group C	0.431	0.281–0.663	< 0.001	0.407	0.253–0.654	< 0.001
Sorafenib administration period (second half *vs* first half)	1.205	0.840–1.728	0.311	-	-	-

AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; HBV: Hepatitis B virus; ECOG: Eastern Cooperative Oncology Group.

DISCUSSION

We investigated the effect of cooperation between oncologists and pharmacists on the prognosis of patients with advanced HCC treated with sorafenib monotherapy. In the present study, the occurrence of HFSR was associated with improved patient prognosis, and this improvement was significantly enhanced by appropriate medication adherence. Close cooperation between oncologists and pharmacists increased adherence, and a strong correlation was observed between OS and TTF.

Several studies have indicated that the emergence of HFSR is associated with prolonged survival in patients with advanced HCC treated with sorafenib[5,6,21]. However, these studies did not evaluate the correlation between medication adherence and survival after the appearance of an AE, including HFSR. Targeted therapies, including sorafenib, can result in unexpected AEs that do not occur after the administration of earlier chemotherapy drugs[22]. Oncologists must recognize these novel AEs at an early stage and provide appropriate treatment to the extent possible. However, previous studies revealed that optimal AE management requires considerable experience and time[7,23]. Management of sorafenib-related AEs includes data collection for AE grading, patient education, and determination of the appropriate sorafenib dose by an oncologist[15].

The use of sorafenib is associated with various AEs, including gastrointestinal, constitutional, or dermatologic events[1,2], and their management may require dose reduction or temporary discontinuation to avoid sorafenib treatment cessation. For example, an appropriate sorafenib dose reduction yielded a decreased rate of permanent discontinuation due to AEs[7]. However, in many patients, these dose changes do not mitigate intolerable or severe AEs, and permanent sorafenib discontinuation is required[24].

Table 7 Prognostic factors of time-to-treatment failure by multivariable Cox regression analysis

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (within 70 yr)	1.059	0.747–1.501	0.747	-	-	-
Male	0.926	0.625–1.372	0.703	-	-	-
Etiology (HBV)	1.208	0.768–1.901	0.413	-	-	-
BCLC stage C	1.311	0.921–1.866	0.132	-	-	-
Portal vein thrombosis	1.379	0.925–2.056	0.115	1.011	0.662–1.545	0.958
Diarrhea	0.675	0.473–0.965	0.031	0.654	0.449–0.952	0.027
Hypertension	1.070	0.735–1.556	0.725	-	-	-
ECOG Performance status 1	0.687	0.446–1.058	0.089	0.725	0.463–1.135	0.159
Group B *vs* Group A	1.670	1.034–2.698	0.036	1.694	1.044–2.748	0.033
Group C *vs* Group A	0.495	0.328–0.747	< 0.001	0.529	0.346–0.811	0.003
Sorafenib administration period (second half *vs* first half)	0.980	0.694–1.384	0.908	-	-	-

AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; HBV: Hepatitis B virus; ECOG: Eastern Cooperative Oncology Group.

Table 8 Prognostic factors of proportion of days covered by logistic regression analyses

	Adjusted analyses		
	OR	95%CI	*P* value
Male	0.352	0.141–0.877	0.025
Child-Pugh stage B	3.830	1.180–12.400	0.025
Diarrhea	0.472	0.198–1.120	0.089
Group B *vs* Group A	0.113	0.036–0.356	< 0.001
Group B *vs* Group C	0.091	0.031–0.266	< 0.001

In our study, only the mutual cooperation system promoted dose reduction after an AE and extended the TTF. In the mutual cooperation system, pharmacists were responsible for collecting data on AE grades, educating patients, and managing any leftover medicine. Furthermore, they documented their findings in a report for the oncologist. On the other hand, in the nonmutual cooperation system, an oncologist examined the patient before pharmacists were involved in patient management. Oncologists were required to evaluate AE grading data, educate patients, and determine the appropriate sorafenib dose. Only after the medical examination did a pharmacist provide additional patient management, and their findings were not reported to the oncologist. In the nonmutual cooperation system, the oncologist had to obtain a substantial amount of information to maintain or revise the sorafenib treatment regimen within 5 to 10 min.

Given these differences between the systems, our results suggest that the mutual cooperation system led to appropriate dose reductions, as reflected by the extended TTF. However, we do not recommend starting sorafenib at half the standard dose (800 mg/d). Dose reductions were guided by the results obtained by the mutual coope-ration system. Additionally, we demonstrated that the best outcomes occur when optimal dosing and good medication adherence are achieved early in the course of sorafenib treatment. In our study, only the mutual cooperation system ensured good adherence in patients who experienced HFSR secondary to sorafenib treatment and prevented unnecessary permanent medication discontinuation.

A previous study showed that despite dramatic improvements in adjuvant hormo-nal therapy for breast cancer, nonadherence, early discontinuation, and effective cancer treatment are affected by treatment-related toxicity, and appropriate inter-ventions are needed to improve breast cancer survival[25]. Another cohort study indicated that long-term tamoxifen therapy for breast cancer reduced the risk of death,
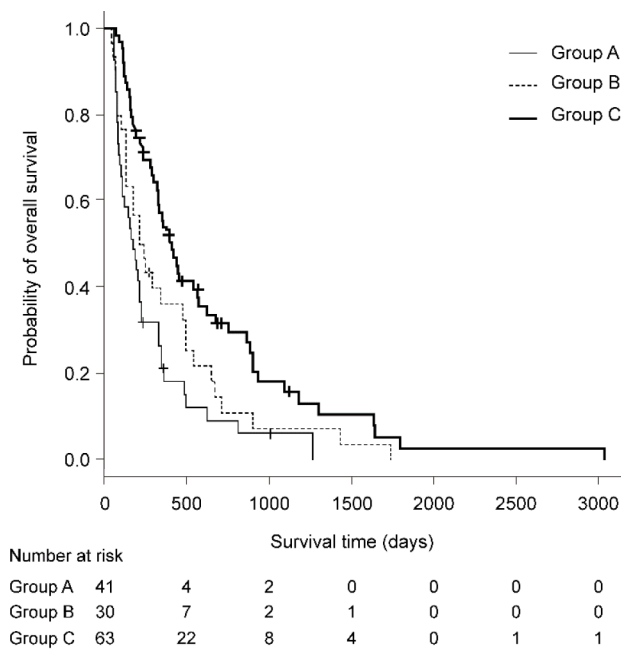
Figure 1 Kaplan-Meier estimates and prognostic factors of overall survival (comparison between each group). Group A, patients without hand-foot skin reaction (HFSR) but with pharmacist intervention; Group B, patients with HFSR and the nonmutual cooperation system; Group C, patients with HFSR and intervention by pharmacists who shared interview information with the oncologist (mutual cooperation system).
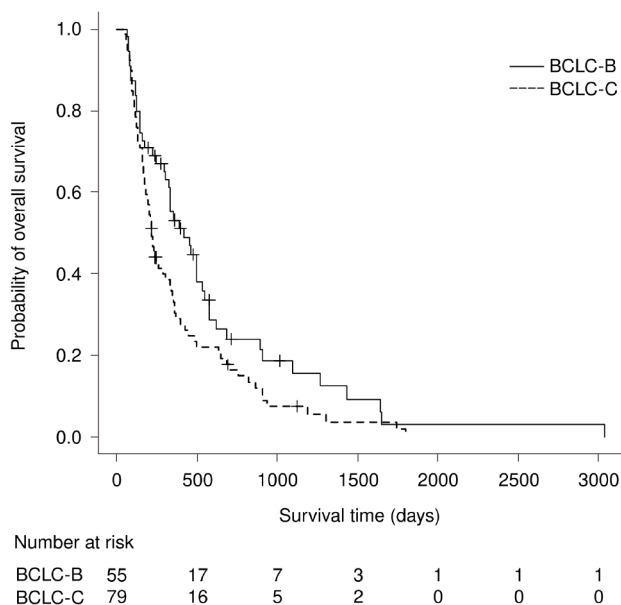
Figure 2 Kaplan-Meier estimates and prognostic factors of overall survival (Barcelona Clinic Liver Cancer B *vs* Barcelona Clinic Liver Cancer C). BCLC: Barcelona Clinic Liver Cancer.

while the risk of death increased with a low adherence rate[26]. In our study, the medical team continued sharing patient information after the patient started taking sorafenib; therefore, the mutual cooperation system enabled the medical team to prevent HFSR or promptly provide patient management, as appropriate. In contrast, the nonmutual cooperation system did not allow patient information to be shared at an early stage; thus, the medical team was not able to take measures to prevent HFSR or plan palliation care in a timely manner. The differences in the effectiveness of HFSR prevention and palliation between the two systems highlight the importance of the various hurdles that can affect medication adherence.

Hurdles to medication adherence are complex and include patient-, clinician-, and healthcare system-related factors. Patient-related factors, such as limited involvement in the treatment decision-making process, poor health literacy, doubts about

Figure 3 Proportion and prognostic factors of nonadherence. Group A, patients without hand-foot skin reaction (HFSR) but with pharmacist intervention; Group B, patients with HFSR and the nonmutual cooperation system; Group C, patients with HFSR and intervention by pharmacists who shared interview information with the oncologist (mutual cooperation system).
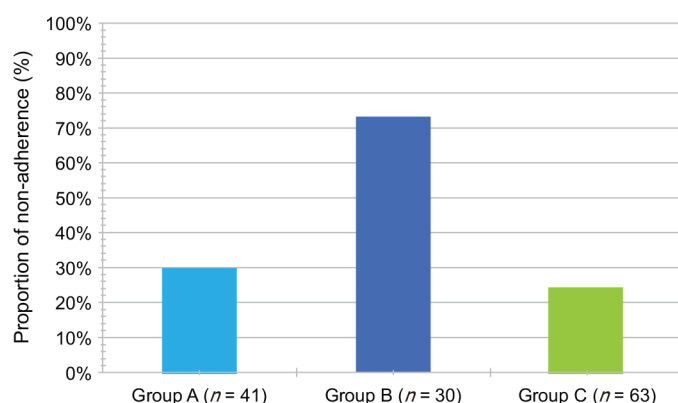
medication effectiveness, and previous adverse effects, influence adherence. Clinician-related factors include failure to recognize nonadherence, poor patient communication, and inadequate multidisciplinary communication between oncologists and pharmacists. Healthcare system-related factors include relationships with clinicians and clinicians' satisfaction with patient care[27,28]. Thus, multiple factors may become hurdles to improving adherence. The mutual cooperation system coordinates interactions among patients, clinicians, and the health system, thereby minimizing barriers to adherence.

Surprisingly, this study revealed that the prognostic value of HFSR was enhanced by appropriate medication adherence. On the other hand, BCLC-B HCC was an independent predictor of improved OS[29]. BCLC stage did not affect the difference in OS between Groups A and C, as there was no significant between-group difference in the baseline stage distribution.

We have reasonable evidence to confirm the validity of our results. First, variables such as age, sex, etiology, ECOG performance status, liver function, comorbidities, and TACE procedure count were not significantly different between the groups. Second, we verified that all patients had received sorafenib monotherapy and no subsequent chemotherapy; therefore, neither our patients' prognoses nor the prolonged OS we observed was affected by other chemotherapeutic agents.

Nevertheless, our study has a few limitations. First, our study design was based on the mutual cooperation system. After a patient was first checked by a specialized pharmacist, the oncologist determined whether to prescribe sorafenib based on the pharmacist's report. However, patients were not required to participate in the mutual cooperation system, and involvement was subject to the patient's wish. After the patients underwent a medical examination by an oncologist, a specialized pharmacist could also provide patient guidance about sorafenib. While patients who were unwilling to participate in the mutual cooperation system may have been included in Group A or B, it is unknown whether this enrollment could have affected the adherence rate. Second, OS and TTF were higher in the mutual cooperation system group (Group C) than in Group A and Group B. It is difficult to determine whether these results were caused by improved adherence or the mechanism underlying the prognostic efficacy of HFSR.

CONCLUSION

The mutual cooperation system increased treatment duration and improved prognosis in patients with HFSR secondary to sorafenib treatment. Additionally, the mutual cooperation system allowed us to promptly initiate sorafenib treatment. Our study clearly demonstrates the clinical and research benefits of this system. The mutual cooperation system for sorafenib treatment management described in this study could be applied to the management of patients treated with other multikinase inhibitors to extend OS. The increased OS resulting from the mutual cooperation system could have a substantial impact on the design of clinical studies in which sorafenib is used as the control drug. Additionally, nonadherence may have adversely affected OS in previous studies, leading researchers to underestimate drug efficacy. We propose that future

clinical investigations designed to improve medication adherence could eliminate OS underestimation.

ARTICLE HIGHLIGHTS

Research background

Although sorafenib prolongs overall survival (OS) in patients with hepatocellular carcinoma (HCC), the drug is associated with various adverse events (AEs) that may lead to permanent discontinuation.

Research motivation

The authors postulated that mutual cooperative intervention for AEs could improve OS in patients with HCC.

Research objectives

The aim of this study is to clarify the association between AE interventions and patient prognosis.

Research methods

The authors developed a mutual cooperation system that was initiated at the start of sorafenib treatment to manage AEs effectively. The system entailed pharmacist consultations during which patients were provided accurate information about sorafenib to alleviate fear and anxiety related to AEs. We stratified patients into three groups: Group A, patients without hand-foot skin reaction (HFSR) but with pharmacist intervention; Group B, patients with HFSR and pharmacist interventions unreported to oncologists (nonmutual cooperation system); and Group C, patients with HFSR and pharmacist interventions known to oncologists (mutual cooperation system).

Research results

The authors enrolled 134 patients (Group A, n = 41; Group B, n = 30; Group C, n = 63). The median OS significantly differed between Groups A and C (6.2 *vs* 13.9 mo, P < 0.01) but not between Groups A and B (6.2 *vs* 7.7 mo, P = 0.62). Group A *vs* Group C was an independent OS predictor (HR, 0.41; 95%CI: 0.25–0.66; P < 0.01). In Group B alone, the time to treatment failure (TTF) was significantly shorter, while the nonadherence rate was higher (P < 0.01). Additionally, Spearman's rank correlation coefficients between OS and TTF in each group were 0.41 (Group A; P < 0.01), 0.13 (Group B; P = 0.51), and 0.58 (Group C; P < 0.01). There was a highly significant correlation between OS and TTF in Group C. However, there was no correlation between OS and TTF in Group B.

Research conclusions

The mutual cooperation system increased the treatment duration and improved the prognosis of patients with HFSR.

Research perspectives

Future prospective studies (*e.g.*, randomized controlled trials) and improved adherence could help avoid OS underestimation.

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