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Intrahepatic Tumor Burden as a Novel Factor Influencing the Introduction of Second-line Chemotherapy for Hepatocellular Carcinoma

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Abstract. *Background/Aim: To examine the factors influencing the introduction of the second-line chemotherapy and discuss the selection of first-line agent for hepatocellular carcinoma (HCC). Patients and Methods: We retrospectively studied 154 patients with HCC who received sorafenib therapy. Results: A total of 109 (70.8%) patients, maintained Child-Pugh grade A and Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤1 upon sorafenib discontinuation. Multivariate analysis revealed that the up-to-seven criteria status in the hepatic lesion [p=0.019; odds ratio=OR, 2.685], albumin–bilirubin (ALBI) grade (p=0.002; OR=3.589), and macroscopic vascular invasion (MVI) (p=0.008; OR=2.972) were significant factors at sorafenib initiation that influenced the maintenance of Child-Pugh grade A and ECOG-PS ≤1 upon therapy discontinuation. Conclusion: Not only ALBI grade and MVI, but also up-to-seven criteria status in the hepatic lesion influence the introduction of second-line therapy, and could affect the selection of the first-line therapy.*

Sorafenib has demonstrated survival benefits in patients with advanced hepatocellular carcinoma (HCC) in pivotal phase III trials (1, 2), and was introduced in 2009 as a first-line systemic chemotherapeutic agent for HCC. Since then, all phase III studies investigating first- and second-line therapies for improving the overall survival (OS) of HCC patients have failed. Therefore, the era of sorafenib alone continued for a long time.

However, regorafenib has been found to significantly improve OS compared to placebo in the RESORCE study (3); therefore, in 2017, it was approved as a second-line systemic chemotherapeutic agent for HCC. According to further analysis of the RESORCE study, the median survival time (MST) of the sorafenib-regorafenib sequential therapy group was 26 months (4). Although inclusion bias was present because, according to the entry criteria, the group in the RESORCE study was switched from sorafenib to regorafenib, it should be noted that sequential therapy is a promising treatment strategy that can improve the prognosis of patients with advanced HCC. In fact, real-world data revealed that sorafenib-regorafenib sequential therapy resulted in favorable OS of HCC patients, and the rate of introduction of subsequent therapy following regorafenib treatment was also high (5, 6). However, sorafenib-regorafenib sequential therapy can only be introduced in limited number of patients who fulfill the RESORCE criteria.

Regarding alternative first-line agents, lenvatinib was approved as a first-line therapy in 2018 based on the results of the REFLECT study in which its non-inferiority to sorafenib was demonstrated in terms of OS (7). The study revealed that lenvatinib yielded higher response rates and longer progression-free survival (PFS) than sorafenib. A post-hoc analysis of the REFLECT study reported that objective response (OR) was an independent predictor of OS (8); therefore, in clinical practice, lenvatinib is often chosen as first-line systemic therapy for HCC with expectations of OR. Thus, lenvatinib seems to be a key drug in systemic therapy for HCC. However, in the REFLECT study, the OS associated

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with lenvatinib was not superior to that associated with sorafenib. Therefore, when deciding the first-line therapy for HCC based on the true endpoint of improving OS, the selection of lenvatinib may not be always optimal.

Conversely, for sorafenib, the OS was well-correlated to patients' post-progression survival (PPS) rather than PFS (9, 10). As the OS does not depend solely on the first-line therapy, therefore, especially for sorafenib therapy, the possibility of sequential therapy may be vital for improving OS in the case of systemic therapy for HCC, and it is essential to clarify the factors associated with the introduction of second-line therapy after sorafenib therapy. Thus, when selecting first-line therapy for patients with HCC, it is crucial to consider whether sequential therapy may be necessary or whether the first-line therapy is the most important key to improve OS.

Additionally, cabozantinib conferred survival benefits in patients who had received sorafenib therapy (11), and ramucirumab conferred survival benefits as second-line therapy subsequent to sorafenib in patients with alpha-fetoprotein (AFP) ≥400 ng/ml (12). Thus, several molecular-targeted agents (MTAs) and sequential therapies are available for HCC treatment. However, these agents are suitable for patients with Child-Pugh A liver function and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1 (13); therefore, not all patients are eligible for sequential therapy. Until now, hepatic reserve and macroscopic vascular invasion (MVI) were the only factors reported to affect the introduction of second-line therapy (14-19). Furthermore, the introduction of second-line therapy is often challenging in patients with high intrahepatic tumor burden in clinical practice because hepatic reserve could decline at first-line therapy termination due to progressive disease.

The purpose of this study was to explore future treatment strategies by examining the possibility of introducing sequential therapy through the analysis of requisite factors, such as hepatic reserve, MVI, and tumor burden, in patients with HCC receiving sorafenib as a first-line therapeutic agent for systemic chemotherapy.

Patients and Methods

Patients with HCC who were initiated with sorafenib therapy between June 2009 and May 2017 were included in this retrospective study. The selection criteria were as follows: 1) Child-Pugh class A disease, 2) ECOG-PS 0 or 1, and 3) treatment with sorafenib monotherapy. In the absence of histological confirmation, cases were diagnosed with HCC if there were no contradictory clinical data in terms of viral status, tumor markers, and radiological findings.

In this retrospective study, we examined the rate of maintenance of Child-Pugh grade A disease and ECOG-PS ≤1, and the factors influencing the deterioration from Child-Pugh A or to ECOG-PS >1 upon sorafenib discontinuation due to refractoriness or intolerance.

Table I. *Characteristics of included patients.*

Age median (range)	69 (36-86)
Gender Male/Female	133/21
ECOG-PS, 0/1	114/40
MVI, Y/N	49/105
EHS, Y/N	104/50
BCLC B/C	27/127
TOR <50%/≥50%	130/24
Up-to-seven criteria status in hepatic lesion within/beyond	77/77
ALB, g/dl median (range)	3.9 (2.9-4.8)
Bil, mg/dl median (range)	0.7 (0.2-2.9)
Child-Pugh score, 5/6	105/49
ALBI grade, 1/2	75/79
AFP, ng/ml median (range)	158 (0.8-331120)
Etiology, HBV/HCV/NBNC	41/58/55
Treatment history, Y/N	137/17
TACE history, Y/N	104/50
Y; TACE number median (range)	4 (1-15)
Sorafenib Initial dose, <800 mg/800 mg	24/130

EOCG-PS: Eastern Cooperative Oncology Group performance status; MVI: macroscopic vascular invasion; Y: yes; N: no; EHS: extrahepatic spread; TOR: tumor occupation ratio to liver; ALB: albumin, Bil: bilirubin; ALBI grade, albumin-bilirubin grade; AFP, alpha-fetoprotein; HBV: hepatitis B virus; HCV: hepatitis C virus; NBNC: non HBV non HCV; TACE: transcatheter arterial chemoembolization. The numerical data represent the numbers of cases or the median values (range).

Although sorafenib therapy was usually initiated at a dose of 800 mg/day, with adverse event (AE)-related dose reductions or interruptions provided if necessary, some patients were administered reduced doses upon treatment initiation at the discretion of the attending physician based on their age, body weight, and the presence/absence of varices. In these patients, dose increases were attempted whenever possible. Although sorafenib therapy was usually continued until an imaging-based diagnosis of progression with drug interruption and dose reduction as needed, some patients promptly discontinued sorafenib therapy without resuming sorafenib with dose reduction, depending on the severity or the kind of AE, even following post-interruption recovery from AEs.

At 6- to 8-week intervals, contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) was performed, and direct antitumor effects and presentation of AEs were assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (20) and Common Toxicity Criteria for Adverse Events version 4.0 (CTCAE v4.0), respectively.

For statistical analysis, the Kaplan–Meier method for OS and time to treatment failure (TTF), chi-square test, and Cox regression analysis were used. Results with $p<0.05$ were considered statistically significant. This study was approved by the institutional review board of our hospital and conformed to the Declaration of Helsinki.

Results

We included 154 patients in this study. The key patient characteristics at the initiation of sorafenib therapy were as follows: macrovascular invasion (MVI), positive (n=49),

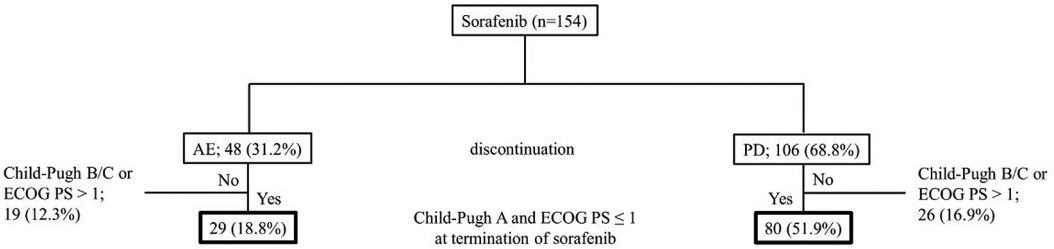

Figure 1. *Summary of clinical course of all patients receiving sorafenib therapy and treatment options for second-line therapy. AE: Adverse event; PD: progressive disease; EOCG PS: Eastern Cooperative Oncology Group performance status.*

negative (n=105); extrahepatic spread (EHS), positive (n=104), negative (n=50); tumor occupation ratio (TOR) in the liver, <50% (n=130), ≥50% (n=24); up-to-seven criteria status (21) in the hepatic lesion, within (n=77), beyond (n=77); Child-Pugh class A, 5 points (n=105), 6 points (n=49); albumin–bilirubin (ALBI), grade I (n=75), II (n=79); and starting dose of sorafenib, <800 mg (n=24), 800 mg (n=130). There were 20 EHS (+) cases without intra-hepatic lesions (Table I).

The MST and median TTF with sorafenib therapy were 10.6 and 2.5 months, respectively. The direct antitumor effects of sorafenib, as measured using the mRECIST, showed an objective response rate and disease control rate of 7.8% and 51.3%, respectively. Figure 1 shows a summary of the clinical course of 154 patients receiving sorafenib in this study. A total of 109 patients (70.8%) maintained Child-Pugh grade A and ECOG-PS ≤1 upon sorafenib discontinuation; details on the sorafenib therapy are shown. The rate of AE-related sorafenib discontinuation was 31.2% (48 of 154 patients). The primary grade ≥3 AEs that led to discontinuation were as follows: hepatobiliary disorders, such as elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT), elevated bilirubin, hepatic encephalopathy, erythema multiforme or intoxication dermatosis, ECOG-PS decrease or general malaise, gastrointestinal tract bleeding, platelet count decrease, hypertension, hand-foot-skin reactions, and diarrhea.

Univariate analysis identified treatment history, MVI, EHS, TOR, up-to-seven criteria status of the intrahepatic lesion, Child-Pugh score, and ALBI grade at the initiation of sorafenib therapy as significant factors that contributed to the maintenance of Child-Pugh grade A and ECOG-PS ≤1 upon sorafenib discontinuation (Table II). Further, two multivariate analyses were performed because TOR and the up-to-seven criteria status in the hepatic lesion were possible confounders. That is, multivariate analysis was performed twice, separately inputting the TOR or up-to-seven criteria status in the hepatic lesion in addition to the ALBI grade, MVI, EHS, treatment history, and sorafenib initial dose, the p-values of which were <0.10 in the univariate analysis. Tables III and IV show the results of multivariate analysis of the factors at sorafenib initiation contributing to the maintenance of Child-Pugh grade A and ECOG-PS ≤1 upon sorafenib discontinuation with TOR inputting model and up-to-seven inputting model, respectively.

ALBI grade [p=0.001; odds ratio (OR), 3.818; 95% confidence interval (CI)=1.682-8.667], MVI (p=0.002; OR=3.422; 95%CI=1.549-7.560), and TOR (p=0.027; OR=3.087; 95%CI=1.135-8.396), as well as ALBI grade (p=0.002; OR=3.589; 95%CI=1.571-8.201), MVI (p=0.008; OR=2.972; 95%CI=1.329-6.648) and up-to-seven criteria status in the hepatic lesion (p=0.019; OR=2.685; 95%CI=1.174-6.142) were significant factors.

Table V shows the proportion of patients who maintained Child-Pugh grade A and ECOG-PS ≤1 upon sorafenib discontinuation. In case of three negative factors (*i.e.*, ALBI grade I, MVI (–), and within the up-to-seven criteria), the proportion of patients who maintained Child-Pugh grade A and ECOG-PS ≤1 upon sorafenib discontinuation was as high as 92.3%. In contrast, if all three factors were positive (*i.e.*, ALBI grade II, MVI (+), and beyond the up-to-seven criteria), the proportion of such patients was as low as 32% (8/25). When two of the three factors were positive, the proportion was around 60%, and when only one of the three factors was positive, the proportion was around 80%. On the other hand, in case of TOR ≥50% that is very high tumor burden, the proportion was as low as follows: 80% (4/5) in ALBI grade I and MVI (–), 50% (1/2) in ALBI grade I and MVI (+), 28.6% (2/7) in ALBI grade II and MVI (–), and 30% (3/10) in ALBI grade II and MVI (+).

Discussion

In the present study, we found that, in addition to ALBI grade and the presence of MVI, intrahepatic tumor burden, represented by the up-to-seven criteria, at sorafenib initiation for HCC, also influenced the deterioration from Child-Pugh A or to ECOG-PS >1 upon therapy termination,

Table II. *Univariate analysis of factors influencing deterioration from Child-Pugh A or to EOCG-PS >1 upon the termination of sorafenib therapy.*

Factor	Number	Child-Pugh A maintained	*p*-Value
Age			
≤69	82	57	0.858
≥70	72	51	
Gender			
Male	133	94	0.709
Female	21	14	
ECOG-PS			
0	114	83	0.220
1	40	25	
Child-Pugh score			
5	105	84	<0.001*
6	49	24	
ALBI grade			
1	75	64	<0.001*
2	79	44	
MVI			
N	105	84	<0.001*
Y	49	24	
EHS			
N	50	29	0.023*
Y	104	79	
TOR			
<50%	130	98	0.001*
≥50%	24	10	
Up-to-seven			
Within	77	65	<0.001*
Beyond	77	43	
Treatment history			
N	17	8	0.028*
Y	137	100	
TACE history			
N	50	33	0.438
Y	104	75	
Etiology			
HBV	41	30	0.406
HCV	58	37	
NBNC	55	41	
AFP, ng/ml			
<400	88	64	0.416
≥400	65	44	
Sorafenib initial dose			
800 mg	130	95	0.063
<800 mg	24	13	

EOCG-PS: Eastern Cooperative Oncology Group performance status; ALBI grade: albumin-bilirubin grade; MVI: macroscopic vascular invasion; N: no; Y: yes; EHS, extrahepatic spread; TOR: tumor occupation ratio to liver; TACE: transcatheter arterial chemoembolization; HBV: hepatitis B virus; HCV: hepatitis C virus; NBNC: non HBV non HCV; AFP: alpha-fetoprotein; *statistically significant.

affecting the introduction of second-line therapy because MTAs for HCC are suitable for patients with Child-Pugh A and ECOG-PS ≤1.

The current era of molecular-targeted therapy for HCC has enabled the use of second- and third-line chemotherapy in addition to first-line therapy for advanced HCC. Therefore, future treatment goals should include the establishment of effective strategies to improve the prognoses of patients with advanced HCC. When choosing first-line therapy for HCC from the perspective of the real goal—improvement of OS—rather than the antitumor effect of the selected drug itself, the integrative treatment strategy, including the sequential therapies used, could be critical as OS is correlated to PPS rather than PFS (9, 10). Hiraoka *et al*. have recently reported that the OS associated with systemic chemotherapy for HCC was significantly correlated to the duration of the administration of all MTAs (22). Thus, to improve OS in HCC it may be essential to use the available MTAs for which there is evidence, that is, establish effective sequential therapies.

However, not all patients can receive sequential therapies because the indication includes a good hepatic reserve and ECOG-PS. When sequential therapy cannot be provided under certain situations in clinical practice, lenvatinib is more likely to be selected as the first-line systemic therapeutic agent than sorafenib to achieve a high response rate and favorable PFS. This is because in such cases, PPS is probably shorter, which may result in the stronger relationship between OS and PFS. In contrast, when second-line therapy can be used, the relationship between OS and PPS will be strengthened. Thus, its introduction should be attempted because the acquisition of good PPS could lead to improvement of OS. Current evidence for sequential therapy for HCC is limited to cases receiving sorafenib as a first-line therapeutic agent; therefore, sorafenib may be selected for first-line therapy if a sequential therapy with hard evidence is planned. In this study, the cases receiving sorafenib in first-line therapy were examined, and we found that the proportion of candidates for second-line therapy was 70.8%. As lenvatinib is currently often introduced as first-line therapy, there are hopes that second-line therapy after lenvatinib may also prove effective in clinical practice in the near future.

In this study, we aimed to examine the proportion of patients who maintained Child-Pugh grade A disease and ECOG-PS ≤1, and the factors contributing to its maintenance upon sorafenib discontinuation due to refractoriness or intolerance when sorafenib was administered as the first-line systematic chemotherapeutic agent for HCC. Ogasawara *et al*. (14) have reported the successful use of second-line systemic chemotherapy in patients with a Child-Pugh score of 5 at the start of sorafenib therapy. In addition, regarding the possibility of the use of regorafenib, Terashima *et al*. (15) and Kuzuya *et al*. (16) have also identified Child-Pugh score as a significant factor in patients who received sorafenib as first-line therapy. Moreover, Yukimoto *et al*. (17) have reported that the ALBI grade or score was a good indicator of the possibility of the introduction of second-line therapy after sorafenib for HCC. Similarly, univariate analysis

Table III. *Multivariate analysis of factors influencing deterioration from Child-Pugh A or to ECOG-PS>1 upon the termination of sorafenib therapy; TOR model.*

Factor	Number	Odds ratio	95%CI	*p*-Value
ALBI grade				
1	75	3.818	1.682-8.667	0.001*
2	79			
TOR				
<50%	130	3.087	1.135-8.396	0.027*
≥50%	24			
MVI				
N	105	3.422	1.549-7.560	0.002*
Y	49			
EHS				
N	50			
Y	104			
Treatment history				
N	17			
Y	137			
Sorafenib initial dose				
800 mg	130			
<800 mg	24			

ALBI grade: Albumin-bilirubin grade; MVI: macroscopic vascular invasion; N: no; Y: yes; EHS: extrahepatic spread; TOR: tumor occupation ratio to liver; CI: confidence interval. *statistically significant.

Table IV. *Multivariate analysis of factors influencing deterioration from Child-Pugh A or to ECOG-PS>1 upon the termination of sorafenib therapy; up-to-seven model.*

Factor	Number	Odds ratio	95%CI	*p*-Value
ALBI grade				
1	75	3.589	1.571-8.201	0.002*
2	79			
Up-to-seven				
Within	77	2.685	1.174-6.142	0.019*
Beyond	77			
MVI				
N	105	2.972	1.329-6.648	0.008*
Y	49			
EHS				
N	50			
Y	104			
Treatment history				
N	17			
Y	137			
Sorafenib initial dose				
800 mg	130			
<800 mg	24			

ALBI grade: Albumin-bilirubin grade; MVI: macroscopic vascular invasion; N: no; Y: yes; EHS: extrahepatic spread; CI: confidence interval. *statistically significant.

Table V. *Proportion of patients who maintained Child-Pugh A and ECOG-PS ≤1 upon sorafenib discontinuation*

Status of each factor at sorafenib introduction			Number of risk factors	The rate of maintenance of Child-Pugh A and ECOG-PS≤1 at sorafenib discontinuation
ALBI; 1,2	MVI; (–), (+)	UT7; W, B		
1	(–)	W	0	36/39 (92.3%)
1	(–)	B	1	16/18 (88.9%)
2	(–)	W	1	19/24 (79.2%)
1	(+)	W	1	6/8 (75%)
2	(+)	W	2	4/6 (66.7%)
1	(+)	B	2	6/10 (60%)
2	(–)	B	2	13/24 (54.2%)
2	(+)	B	3	8/25 (32%)

ALBI grade: Albumin-bilirubin grade; MVI: macroscopic vascular invasion; UT7: up-to-seven; W: within; B: beyond.

revealed that the Child-Pugh score and ALBI grade were both significant factors in this study. ALBI grade may be more useful than the Child-Pugh score in terms of objectivity because it can be calculated using only the actual objective measures (*e.g.*, albumin and bilirubin levels) (23). Therefore, in this study, only the ALBI grade was selected for the multivariate analysis because Child-Pugh score and ALBI grade could be confounders.

Multivariate analyses identified that, in addition to the ALBI grade, MVI and either TOR or the up-to-seven criteria status of the intrahepatic lesion were also significant factors. Regarding the possibility of the use of regorafenib, Uchikawa *et al*. (18) and Terashima *et al*. (15) have identified MVI (+) as a significant factor in patients who received sorafenib for first-line therapy, consistent with our results.

To the best of our knowledge, this study is the first to demonstrate that the TOR or up-to-seven criteria status in the hepatic lesion influences the deterioration from Child-Pugh A or to ECOG-PS >1 upon sorafenib discontinuation. Although a TOR <50% or ≥50% was not a significant

predictive factor in Uchikawa's study, it may be clinically acceptable that the Child-Pugh score would worsen at the time of tumor progression during sorafenib treatment if the intrahepatic tumor burden is high. In contrast, it is likely that second-line therapy can be introduced in patients with relatively low intrahepatic tumor burden such as those within up-to-seven criteria, which may be also clinically acceptable. In cases beyond the up-to-seven criteria, the range of intrahepatic tumor burden is wide, from relatively low to TOR ≥50%. Thus, when the intrahepatic tumor burden is not so high, second-line therapy after sorafenib would be feasible to some degree, however, the possibility of introducing second-line therapy after sorafenib significantly decreases if the ALBI grade II or MVI (+) is added (Table V). Although our study has revealed that up-to-seven criteria in the hepatic lesions is a key indicator influencing the introduction of second-line chemotherapy, this should be further verified in the future.

Although the results of the current study may lead to the use of lenvatinib as a first-line therapeutic agent in cases with a high tumor burden owing to difficulties in introducing sequential therapy when sorafenib is used in first-line treatment, no studies have reported the safety and benefits of lenvatinib in patients with a TOR ≥50%, as a TOR ≥50% was an exclusion criterion in the REFLECT trial. As a previous study has found no significant differences in the effects of sorafenib between groups with TOR ≥50% and <50% (24), it may be appropriate to use sorafenib for first-line therapy. However, it may be difficult to introduce second-line molecular-targeted therapy after sorafenib therapy with improved OS. Therefore, future studies should evaluate the safety and benefits of lenvatinib in such patients.

The present study showed that it may be easier to administer systemic chemotherapy in anticipation of sequential therapy in patients with ALBI grade I, MVI(–), and a low intrahepatic tumor burden, for example, those within the up-to-seven criteria in the hepatic lesion at the start of first-line therapy if sorafenib is the selected agent. For such patients, sorafenib may be more suitable for first-line therapy as there are useful second-line therapies, after sorafenib, for which hard evidence established through phase III clinical trials allow anticipation of better prognoses (3, 11, 12). Although there is no evidence for the use of lenvatinib as a second-line therapy after sorafenib, it can also be introduced. Moreover, it has recently been reported that lenvatinib was introduced at a high rate as a third-line therapy after regorafenib had been introduced as second-line therapy (5, 6). Additionally, it has recently been reported that the efficacy of lenvatinib was similar when used in first-, second-, or later-line therapy (25). Thus, sorafenib may be used as first-line therapy in patients with ALBI grade I, MVI(–), and a low intrahepatic tumor burden. Of course, in patients with these characteristics at the start of first-line therapy, sequential therapy may easily be introduced, even if lenvatinib is used as the first-line treatment agent. However, at present, no sequential therapy regimen with lenvatinib as first-line therapy has been established, and we recommend that it should be examined in the future. In contrast, for patients with ALBI grade II, MVI(+), or a high intrahepatic tumor burden, for example, those beyond the up-to-seven criteria in the hepatic lesion at the start of the first-line therapy, lenvatinib may be more suitable for use as a first-line therapy in the anticipation of high response rates and better PFS values because it may be difficult to treat with a view to the introduction of second-line therapy, especially in sorafenib treatment. As described above, the status of these three factors could affect the decision on the appropriate first-line therapy for HCC.

This study has a few limitations that are worth highlighting. First, this was a single-facility, retrospective study with a small sample size. Second, the starting dosage of sorafenib and discontinuation criteria were determined at the discretion of the attending physician. Future studies should include multiple institutions. In this study, we analyzed patients receiving sorafenib as a first-line therapeutic agent; however, lenvatinib has also been introduced as a first-line agent with expectations of a higher response rate and PFS. Therefore, it may be clinically important to examine the outcomes of therapy with lenvatinib as the first-line agent and sequential therapies after lenvatinib therapy, and to compare the outcomes between lenvatinib and sorafenib.

In conclusion, in addition to the ALBI grade and MVI, intrahepatic tumor burden, represented by the TOR or up-to-seven criteria at sorafenib initiation for HCC, also influences the deterioration from Child-Pugh A or to ECOG-PS >1 upon therapy termination, leading to difficulties in initiating second-line therapy and possibly influencing the decision making regarding first-line therapy. Further studies are required to validate our results.

Conflicts of Interest

Yoshito Itoh received lecture fees from Bristol-Myers Squibb Company and Merck Sharp and Dohme, as well as commercial research funding from Bayer AG, Eisai Co., Ltd., Bristol-Myers Squibb Company and Merck Sharp and Dohme. Michihisa Moriguchi received lecture fees from Bayer AG and Eisai Co., Ltd.

Author's Contributions

Conception and design: M.M., T.A., A.T., Y.S.; Provision of study materials or patients: M.M., T.A., R.S, K.I., S.T., K.A., M.E.; Collection and assembly of data: M.M., T.A., R.S, K.I, S.T, K.A., M.E.; Data analysis and interpretation: all Authors; Manuscript writing: M.M. Final approval of manuscript: all Authors.

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