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Liver Function in Older Patients With Unresectable Hepatocellular Carcinoma After Administration of Lenvatinib

RYU SASAKI[1], MASANORI FUKUSHIMA[1], MASAFUMI HARAGUCHI[1], SATOSHI MIUMA[1], HISAMITSU MIYAAKI[1], MASAAKI HIDAKA[2], SUSUMU EGUCHI[2], SATOSHI MATSUO[3], TOSHIHISA MATSUZAKI[3], SATSUKI HASHIMOTO[4], KAZUO OHBA[4], YUKI KUGIYAMA[5], HIROSHI YATSUHASHI[5], HIDETAKA SHIBATA[6], YASUHIDE MOTOYOSHI[7], MASAYA SHIGENO[8], SHINICHI IWATSU[9], YUJI KATO[9], NOBORU KINOSHITA[10] and KAZUHIKO NAKAO[1]

[1]*Department of Gastroenterology and Hepatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan;*
[2]*Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan;*
[3]*Gastroenterology and Hepatology, Sasebo City General Hospital, Sasebo, Japan;*
[4]*Gastroenterology and Hepatology, Japan Community Health Care Organization, Isahaya, Japan;*
[5]*Clinical Research Center, National Hospital Organization, Omura, Japan;*
[6]*Gastroenterology and Hepatology, Shibata Chokodo Hospital, Shimabara, Japan;*
[7]*Gastroenterology and Hepatology, Nagasaki Harbor Medical Center, Nagasaki, Japan;*
[8]*Gastroenterology and Hepatology, Japanese Red Cross, Nagasaki, Japan;*
[9]*Gastroenterology and Hepatology, Oita Prefectural Hospital, Oita, Japan;*
[10]*Gastroenterology and Hepatology, Sasebo Chuo Hospital, Sasebo, Japan*

Abstract. *Background: The age of patients with advanced hepatocellular carcinoma (HCC) eligible for molecular-targeted drug treatment is increasing. We assessed liver function after lenvatinib administration according to age in patients with advanced HCC. Patients and Methods: In this retrospective, multicenter, observational study, we reviewed the records of patients with HCC who received lenvatinib treatment (March 2018-March 2020). Liver function was measured using the Albumin-Bilirubin Index (ALBI). Results: Of 119 patients, with a median age of 72.0 years, median overall survival was 15.3 months. Overall survival was significantly better in the group which maintained liver function (p=0.02). Older age (≥72 years) was associated with liver-function deterioration within 8 weeks (odds ratio=2.47, 95% confidence interval=1.06-5.75, p=0.035). The ALBI score was significantly higher in the older group at 4 and 8 weeks after lenvatinib administration. Conclusion: Lenvatinib administration was more likely to adversely affect liver function in older patients; dose adjustment should be considered in such patients.*

wCorrespondence to: Ryu Sasaki, Department of Gastroenterology and Hepatology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki City, Nagasaki 852-8501, Japan. Tel: +81 958197481, Fax: +81 958197482, e-mail: r.sasaki@nagasaki-u.ac.jp

Key Words: Hepatocellular carcinoma, older age, unresectable tumor, relative dose intensity, molecular target agents.

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, including in the Asia-Pacific region (1, 2), notwithstanding the improvement in prognosis in recent years given the advances in early diagnosis and treatment. Therefore, the age of patients with advanced HCC who are eligible for molecular-targeted drug treatment is increasing (3). Systemic therapy using molecular targeted agents is recognized as an effective treatment option for advanced unresectable HCC (4). Lenvatinib is a key drug for advanced HCC and has been shown to have high therapeutic efficacy in clinical practice (5-8). However, some patients experience rapid deterioration of liver function and have a poor prognosis. The purpose of this study was to evaluate the relationship between liver function after lenvatinib administration and patient age.

Patients and Methods

Patients. We retrospectively reviewed the records of 154 patients with HCC treated with lenvatinib at Nagasaki University Hospital and its related facilities between March 2018 and March 2020. Patients with an administration period <28 days (n=21) or incomplete records (n=14) were excluded, leaving the data of 119 patients for the analysis.

Treatment protocol. Patients with unresectable HCC were administered lenvatinib (Lenvima; Eisai Co., Ltd., Tokyo, Japan) orally. The standard dose for patients weighing more than 60 kg was 12 mg/day. The standard dose for patients weighing less than 60 kg and those with Child–Pugh class B was 8 mg/day. Decisions regarding dose reduction and discontinuation of lenvatinib were made by the individual clinician according to the lenvatinib administration guidelines. Lenvatinib continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Evaluation criteria for response and adverse events. Treatment response was evaluated using contrast-enhanced computed tomography or magnetic resonance imaging in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) (9) and modified Response Evaluation Criteria in Solid Tumors (mRECIST) (10). Tumors were evaluated every 8-12 weeks, and the best response was regarded as the therapeutic effect. Drug-related adverse events (AEs) were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (11).

Assessment of liver function and relative dose intensity (RDI). Liver function was evaluated using the Albumin-Bilirubin (ALBI) score and Modified Albumin-Bilirubin grade (mALBI) (12-14). The ALBI score with grading was defined as follows: Grade 1, ≤−2.60; grade 2a, >−2.60 to −2.27; grade 2b, ≤−2.27 to ≤−1.39; and grade 3, >−1.39. Deterioration of liver function was defined as an increase in the mALBI grade within 8 weeks. The RDI was calculated by dividing the actual lenvatinib dose by the standard dose according to the patient's body weight and liver function.

Statistical analysis. The median for continuous variables was used to divide patients into two groups. The chi-squared and Fisher's exact tests were used to compare categorical variables. Comparisons between groups of continuous variables were performed using the Student's *t*-test and Mann–Whitney *U*-test, as appropriate. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Multivariable logistic regression analysis was performed to determine the factors that were associated with a deterioration of liver function. Variables with *p*-values less than 0.05 in the univariate analysis were selected and included in the multivariable logistic regression model. Variables with *p*-values less than 0.05 were considered statistically significant. The data were analyzed using SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA).

Ethical issues. All procedures in this study were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and the ethical standards (institutional and national) of the responsible committee for human experimentation. Informed consent was provided for all patients in advance. The study protocol was approved by the Ethical Committee of Nagasaki University Hospital (confirmation number: 19041523-2).

Table I. *Patient characteristics (N=119)*.

Variable	Value
Age, years	
Median (range)	72.0 (41-89)
Gender, n (%)	
Male	94 (79.0)
Female	25 (21.0)
BMI, kg/m^2	
Median (range)	23.20 (16.5-34.4)
Performance status, n (%)	
0	76 (63.9)
1	39 (32.8)
2	4 (3.3)
Child–Pugh grade, n (%)	
A	98 (82.4)
B	21 (17.6)
mALBI grade, n (%)	
1	30 (25.2)
2a	34 (28.6)
2b	50 (42.0)
3	5 (4.2)
Macroscopic PV invasion (Vp3/4), n (%)	
Present	20 (16.8)
Extrahepatic spread, n (%)	
Present	44 (37.0)
BCLC stage, n (%)	
A	1 (0.8)
B	38 (31.9)
C	80 (67.2)
Etiology, n (%)	
HBV	28 (23.5)
HBC	34 (28.6)
NBNC	57 (47.9)
Platelet count, ×10^4/μl	
Median (range)	13.40 (4.2-47.0)
PT, %	
Median (range)	89.0 (32-135)
T.bil, mg/dl	
Median (range)	0.80 (0.3-2.6)
Albumin, g/dl	
Median (range)	3.60 (2.2-4.7)
ALT, IU/ml	
Median (range)	27.0 (10-198)
AFP, ng/ml	
Median (range)	42.5 (2-89,533)
DCP, mAU/ml	
Median (range)	573.0 (10-990,474)
Systemic therapy, n (%)	
Naïve	96 (80.7)
Experienced	23 (19.3)

AFP: Alpha fetoprotein; ALT: alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer classification; BMI: body mass index; DCP: des-gamma-carboxy prothrombin; HBV: hepatitis B virus; HCV: hepatitis C virus; mALBI: modified Albumin-Bilirubin Index; NBNC: non-hepatitis B- or C-related; PT: prothrombin; PV: portal vein; T.bil: total bilirubin.

Results

Patient characteristics. Table I shows the baseline characteristics of the 119 patients (94 men, 25 women) who were included in this study. The median age of patients at the start of lenvatinib therapy was 72.0 years. Of the 119 patients, 64 (53.8%) had mALBI grade 1 or 2a, 44 (37.0%) had extrahepatic spread, 20 (16.8%) had macroscopic portal vein invasion, and 23 (19.3%) had undergone systemic chemotherapy with sorafenib.

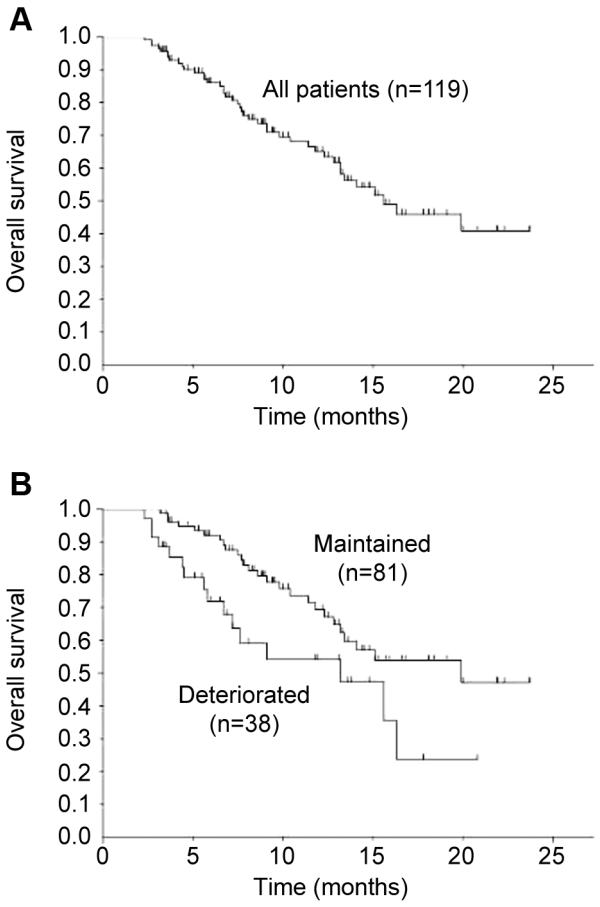

Figure 1. *A: Kaplan–Meier curve of the overall survival of the whole patient cohort. The median overall survival was 15.3 months. B: Kaplan–Meier curves of survival according to change in liver function. Overall survival was significantly better for those whose liver function was maintained in (p=0.024).*

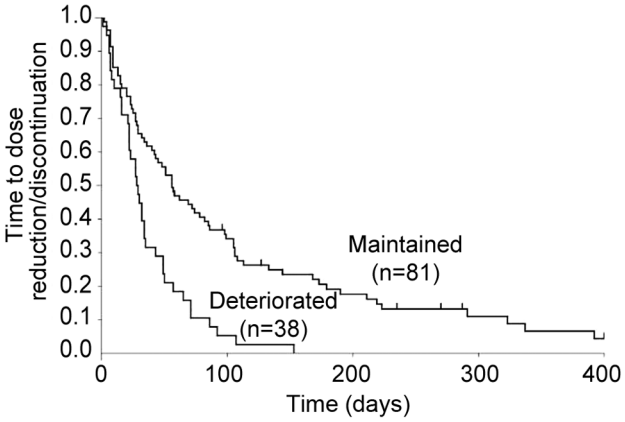

Figure 2. *Kaplan–Meier curves for time to dose reduction or discontinuation stratified by liver function. The time to dose reduction or discontinuation was significantly shorter among patients who experienced deterioration of liver function (p<0.001).*

OS and time to dose reduction or discontinuation of lenvatinib. The median OS was 15.3 months. The OS was significantly longer in the group which maintained their mALBI grade (p=0.024) (Figure 1). The median time to dose reduction or discontinuation was 42 days and was significantly shorter in the patients with deterioration of liver function (p<0.001) (Figure 2).

Baseline factors associated with the deterioration of liver function. In the univariate analysis, three factors were significantly associated with deterioration of liver function within 8 weeks: Age, macroscopic portal vein invasion, and etiology. Older age (≥72 years, odds ratio=2.47, 95% confidence interval=1.06-5.75, p=0.035) was a predictor of the deterioration of liver function within 8 weeks (Table II) in the multivariable logistic regression analysis.

Serial changes in the ALBI score. Figure 3 shows the serial changes in the ALBI score stratified by age. The median ALBI scores in the group age ≥72 years were –2.27, –2.05, –2.06, –2.25, and –2.34 at pretreatment, 4 weeks, 8 weeks, 12 weeks, and 16 weeks, respectively. There was no significant difference in the baseline ALBI score between the older and younger groups. The ALBI score was significantly higher in the older group 4 and 8 weeks after lenvatinib administration, but there was no significant difference between the groups 12 and 16 weeks after lenvatinib administration.

Radiological response. The radiological response rates are shown in Table III. According to RECIST, four patients (3.4%) had a complete response, 18 patients (15.1%) had a partial response (15.1%), and 69 patients (58.0%) had stable disease. The objective response rate (ORR: complete + partial resonse) was 18.5%, and the disease control rate (ORR + stable disease) was 76.5%. The ORR of patients in the younger group was significantly higher than that of the patients in the older group (27.6% *vs*. 9.8%, respectively, p=0.02) but the disease control rate of the younger and older groups did not differ significantly (82.8% *vs*. 70.5%, respectively, p=0.11).

Adverse events. Treatment-emergent AEs during lenvatinib administration are shown in Table IV. Fatigue and reduced appetite were the most common subjective AEs in the older group but there were no differences in the incidence of other AEs according to age.

Relative dose intensity. Figure 4 shows the RDI by week, stratified according to age. The median RDI at 8 weeks in the younger and older age groups was 77.0% and 67.5%,

Table II. *Logistic regression analysis of factors associated with a deterioration of liver function within 8 weeks.*

Factor		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	≥72 years	2.84 (1.26-6.42)	0.01	2.47 (1.06-5.75)	0.03
Gender	Male	1.26 (0.47-3.34)	0.63		
BMI	<23.2 kg/m^2	1.74 (0.79-3.83)	0.16		
Performance status	1 or 2	2.01 (0.91-4.45)	0.08		
Child–Pugh grade	B	1.39 (0.52-3.71)	0.50		
mALBI grade	2b or 3	0.56 (0.25-1.25)	0.16		
Macroscopic PV invasion	Vp3 or 4	0.59 (0.36-0.98)	0.04	0.59 (0.34-1.01)	0.05
Extrahepatic spread	Yes	0.99 (0.44-2.20)	0.98		
BCLC stage	C	0.76 (0.34-1.72)	0.51		
Etiology	NBNC	1.73 (1.03-2.91)	0.03	2.22 (0.96-5.13)	0.05
Platelet count	<13.4 ×104/μl	1.39 (0.64-3.03)	0.39		
PT	<89%	1.05 (0.48-2.27)	0.89		
T.bil	≥0.8 mg/dl	1.75 (0.79-3.87)	0.16		
Albumin	<3.6 g/dl	0.75 (0.34-1.62)	0.46		
ALT	≥27 IU/ml	1.20 (0.55-2.61)	0.63		
AFP	≥42.5 ng/ml	0.87 (0.40-1.89)	0.74		
DCP	≥573 mAU/ml	1.555 (0.714-3.387)	0.265		
Systemic therapy	Experienced	1.173 (0.449-3.065)	0.744		

AFP: Alpha fetoprotein; ALT: alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer classification; BMI: body mass index; CI: confidence interval; DCP: des-gamma-carboxy prothrombin; HBV: hepatitis B virus; HCV: hepatitis C virus; mALBI: modified Albumin-Bilirubin Index; NBNC: non-hepatitis B- or C-related; PT: prothrombin; PV: portal vein; T.bil: total bilirubin.

respectively. After 8 weeks, the younger age group tended to have a significantly higher RDI ($p<0.05$).

Discussion

In this study, we assessed the relationship between liver function after lenvatinib administration and age. Systemic therapy for advanced HCC is rapidly advancing, and lenvatinib is currently the preferred first-line treatment. It has been reported that lenvatinib is highly safe, even in older individuals, and has a limited effect on hepatic reserve (5, 15). The ORR to lenvatinib is high in patients with good liver function, and it is desirable to use it if liver function is maintained. However, in some cases, even if pretreatment liver function is maintained, liver function deteriorates rapidly after lenvatinib administration, and is associated with a poor prognosis (15). The ALBI score is useful as an index for assessing hepatic reserve, particularly in patients with Child–Pugh class A (14). The mALBI grade is a refinement of the ALBI score and is able to detect slight changes in liver function (12). Similar to previous reports, our study revealed that patients who experienced deterioration of liver function within 8 weeks had a poor prognosis.

Age was identified in advance as a factor affecting liver function after lenvatinib administration. In our study, older patients had higher ALBI scores, especially 4 and 8 weeks after initiating therapy, and were more likely to require dose reduction and drug discontinuation in the short term. One of the causes of liver-function deterioration in older patients may be reduced appetite. Compared with younger patients, older patients are more likely to have reduced appetite. Reduced food intake may cause the serum albumin level to decrease. There was no difference in the frequency of AEs

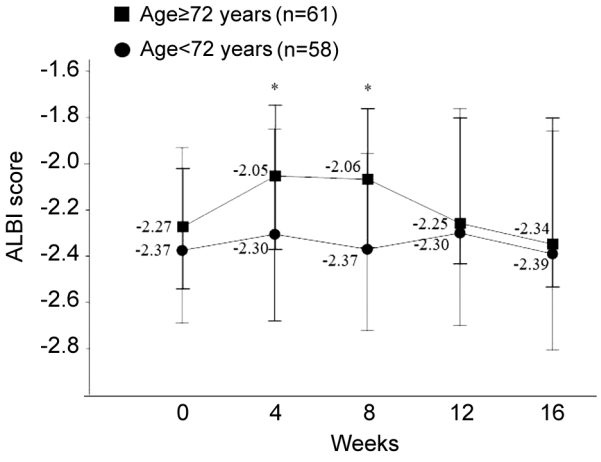

Figure 3. *Serial changes in the Albumin-Bilirubin Index (ALBI) score according to age. The ALBI score differed significantly (*p<0.05) between the age groups at 4 and 8 weeks. Data values are medians, the error bar represents the interquartile range.*

Table III. *Radiological response to lenvatinib therapy.*

	All patients (N=119), n (%)		Age <72 years (N=58), n (%)		Age ≥72 years (N=61), n (%)	
Response category	mRECIST	RECIST	mRECIST	RECIST	mRECIST	RECIST
Complete response	10 (8.4%)	4 (3.4%)	7 (12.1%)	2 (3.4%)	3 (4.9%)	2 (3.3%)
Partial response	45 (37.8%)	18 (15.1%)	26 (44.8%)	14 (24.1%)	19 (31.1%)	4 (6.6%)
Stable disease	37 (31.1%)	69 (58.0%)	15 (25.9%)	32 (55.2%)	22 (36.1%)	37 (60.7%)
Progressive disease	23 (19.3%)	26 (21.8%)	9 (15.5%)	9 (15.5%)	14 (23.0%)	17 (27.9%)
Unknown or not evaluable	4 (3.4%)	2 (1.7%)	1 (1.7%)	1 (1.7%)	3 (4.9%)	1 (1.6%)
Objective response	55 (46.2%)	22 (18.5%)	33 (56.9%)	16 (27.6%)	22 (36.1%)	6 (9.8%)
Disease control	92 (77.3%)	91 (76.5%)	48 (82.8%)	48 (82.8%)	44 (72.1%)	43 (70.5%)

RECIST: Response Evaluation Criteria in Solid Tumors (ver 1.1) (9); RECIST: modified Response Evaluation Criteria in Solid Tumors (11).

Table IV. *Adverse events according to age.*

	All patients (N=119), n (%)		Age <72 years (N=58), n (%)		Age ≥72 years (N=61), n (%)	
Treatment-emergent adverse events	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	76 (63.9%)	14 (11.8%)	38 (65.5%)	6 (10.3%)	38 (62.3%)	8 (13.1%)
Fatigue	72 (60.5%)	2 (1.7%)	33 (56.9%)	0 (0.0%)	39 (63.9%)	2 (3.3%)
Decreased appetite	65 (54.6%)	4 (3.4%)	28 (48.3%)	0 (0.0%)	37 (60.7%)	4 (6.6%)
Proteinuria	51 (42.9%)	10 (8.4%)	25 (43.1%)	2 (3.4%)	26 (42.6%)	8 (13.1%)
Elevated liver enzymes	51 (42.9%)	7 (5.9%)	25 (43.1%)	2 (3.4%)	26 (42.6%)	5 (8.2%)
Hypothyroidism	51 (42.9%)	0 (0.0%)	19 (32.8%)	0 (0.0%)	32 (52.5%)	0 (0.0%)
Palmar–plantar erythrodysesthesia syndrome	44 (37.0%)	1 (0.8%)	28 (48.3%)	1 (1.7%)	16 (26.2%)	0 (0.0%)
Thrombocytopenia	41 (34.5%)	5 (4.2%)	22 (37.9%)	3 (5.1%)	19 (31.1%)	2 (3.3%)
Diarrhea	30 (25.2%)	0 (0.0%)	15 (25.9%)	0 (0.0%)	15 (24.6%)	0 (0.0%)
Weight loss	24 (20.2%)	1 (0.8%)	14 (24.1%)	0 (0.0%)	10 (16.4%)	1 (1.6%)

other than fatigue, reduced appetite, and hypothyroidism between the older and younger groups (Table III). However, this does not mean that there is no difference in the therapeutic response to lenvatinib between older and younger patients. Because AEs appeared sooner, the treatment period was significantly shorter in the older group (Figure 5), and dose reduction or discontinuation was required. Therefore, it cannot be concluded that older and younger patients have a similar incidence of AEs. According to our study, there was no significant difference in the ALBI score after 12 weeks according to age. This does not appear to be attributable to an improvement of liver function in the older group but occurred because patients with worsening liver function dropped out because of drug interruption, and the analysis was limited to patients who were able to continue treatment for a long time without deterioration of liver function.

The RDI was significantly lower for the older group. This is attributable to dose reduction or discontinuation with fatigue and reduced appetite in a short period of time. The lower ORR for the older group than the younger group is likely to have occurred as a result of the reduced RDI (Figure 4). We previously reported that the RDI is important for antitumor efficacy with lenvatinib treatment (16). There are several reports of the significance of the RDI for the antitumor effect of lenvatinib (17, 18). In the older group, it may be difficult to achieve a response, especially if dose reduction or discontinuation of lenvatinib is required because of deterioration of liver function. However, no significant difference was found in the disease control rate according to age. In addition, a previous study revealed no significant difference in OS (15). Therefore, optimal dosage adjustment in older patients is required to obtain the same therapeutic benefits as younger patients.

Some of the older patients experienced rapid deterioration of liver function. In our study, baseline factors other than age were not associated with deterioration of liver function within 8 weeks. When administering lenvatinib to older patients, it may be necessary to adjust the dose to consider the body weight and hepatic reserve.

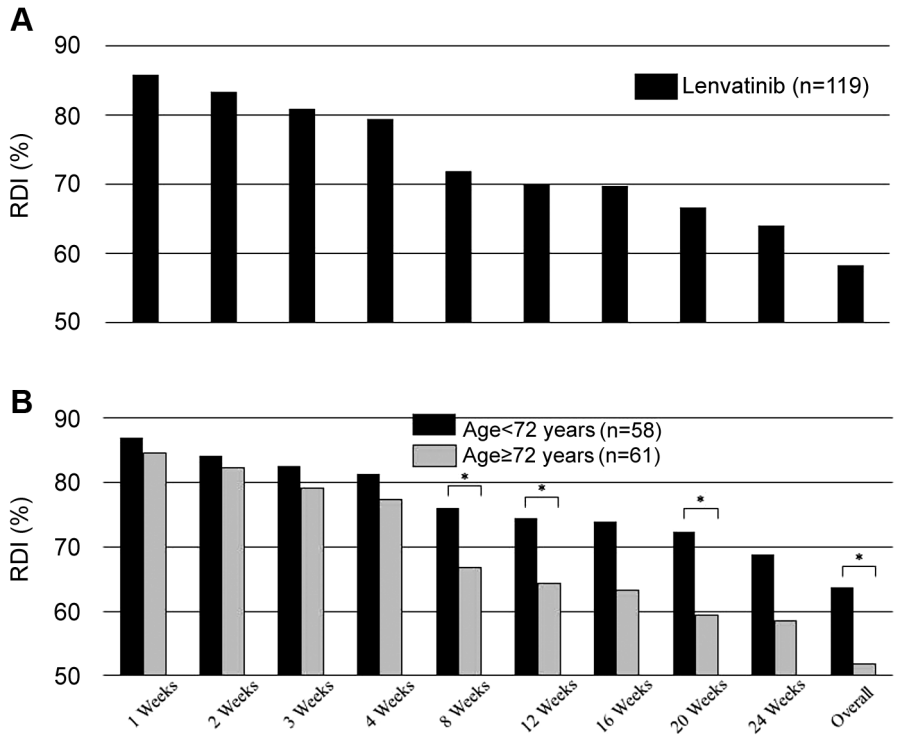

Figure 4. *A: Relative dose intensity (RDI) by week of lenvatinib therapy. The overall RDI was 58.2%. B: RDI by week of lenvatinib therapy according to age. The younger group had a significantly (*p<0.05) higher RDI after 8, 12, and 20 weeks, and overall.*

The relationship between molecular targeted agents and muscle mass has also been reported, and factors other than age may need further investigation (19). Generally, dose reduction is not recommended for maintaining the RDI. However, the use of low RDI treatment in older patients with HCC should be reconsidered as a means of ensuring continuity of lenvatinib treatment. Although new drugs may be used as an alternative to lenvatinib (20), it is inappropriate to select a second-line molecular targeted agent without first considering the use of lenvatinib at a low RDI and short duration for older patients.

Limitations of this study include its retrospective nature and the requirement for the patients to have been administered lenvatinib for 28 days or longer. Patients who were unable to continue lenvatinib for at least 28 days were excluded. Further studies are required with patients who discontinue lenvatinib after a shorter period. However, unlike previous reports of the effects of lenvatinib on older patients, this was the first study to report that age affects liver function. This is an important consideration regarding lenvatinib administration to older patients who are more likely to experience AEs and in whom dose adjustment needs to be considered for an optimal therapeutic effect.

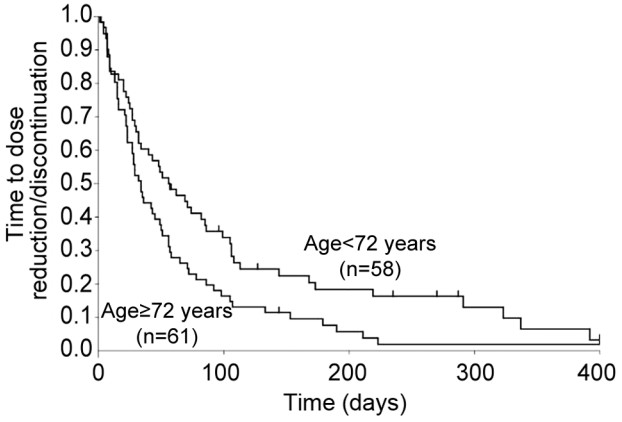

Figure 5. *Kaplan–Meier curves for time to dose reduction or discontinuation stratified by age. The time to dose reduction or discontinuation was significantly shorter in the older age group than in the younger age group (p=0.023).*

Conflicts of Interest

The Authors declare that there are no conflicts of interest in regard to this study.

Authors' Contributions

All Authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by RS, MF, MH, SM, TM, SH, YK, HS, YM, MS, SI, and NK. The first draft of the article was written by RS, and all authors commented on previous versions of the article. All Authors read and approved the final article.

References

1 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH and Marrero JA: AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology *67(1)*: 358-380, 2018. PMID: 28130846. DOI: 10.1002/hep.29086

2 Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK and Sarin SK: Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: A 2017 update. Hepatol Int *11(4)*: 317-370, 2017. PMID: 28620797. DOI: 10.1007/s12072-017-9799-9

3 Kudo M, Izumi N, Kubo S, Kokudo N, Sakamoto M, Shiina S, Tateishi R, Nakashima O, Murakami T, Matsuyama Y, Takahashi A, Miyata H and Takayama T: Report of the 20th nationwide follow-up survey of primary liver cancer in Japan. Hepatol Res *50(1)*: 15-46, 2020. PMID: 31655492. DOI: 10.1111/hepr.13438

4 Kudo M: Systemic therapy for hepatocellular carcinoma: Latest advances. Cancers (Basel) *10(11)*: 2018. PMID: 30380773. DOI: 10.3390/cancers10110412

5 Tada T, Kumada T, Hiraoka A, Michitaka K, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, Takaguchi K, Kariyama K, Itobayashi E, Tajiri K, Shimada N, Shibata H, Ochi H, Toyoda H, Nouso K, Tsutsui A, Nagano T, Itokawa N, Hayama K, Imai M, Joko K, Koizumi Y and Hiasa Y: Safety and efficacy of lenvatinib in elderly patients with unresectable hepatocellular carcinoma: A multicenter analysis with propensity score matching. Hepatol Res *50(1)*: 75-83, 2020. PMID: 31660700. DOI: 10.1111/hepr.13427

6 Ueshima K, Nishida N, Hagiwara S, Aoki T, Minami T, Chishina H, Takita M, Minami Y, Ida H, Takenaka M, Sakurai T, Watanabe T, Morita M, Ogawa C, Hiraoka A, Johnson P and Kudo M: Impact of baseline ALBI grade on the outcomes of hepatocellular carcinoma patients treated with lenvatinib: A multicenter study. Cancers (Basel) *11(7)*: 2019. PMID: 31284682. DOI: 10.3390/cancers11070952

7 Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, Takaguchi K, Kariyama K, Itobayashi E, Tajiri K, Shimada N, Shibata H, Ochi H, Tada T, Toyoda H, Nouso K, Tsutsui A, Nagano T, Itokawa N, Hayama K, Imai M, Joko K, Koizumi Y, Hiasa Y, Michitaka K, Kudo M and Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan).: Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions-multicenter analysis. Cancer Med *8(8)*: 3719-3728, 2019. PMID: 31127698. DOI: 10.1002/cam4.2241

8 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M and Cheng AL: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet *391(10126)*: 1163-1173, 2018. PMID: 29433850. DOI: 10.1016/S0140-6736(18)30207-1

9 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

10 Lencioni R and Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis *30(1)*: 52-60, 2010. PMID: 20175033. DOI: 10.1055/s-0030-1247132

11 Common Terminology Criteria for Adverse Events (CTCAE) v4.0:National Cancer Institute. Protocol development. Cancer therapy evaluation program. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf [Last accessed on 24thFebruary 2021]

12 Hiraoka A, Kumada T, Tsuji K, Takaguchi K, Itobayashi E, Kariyama K, Ochi H, Tajiri K, Hirooka M, Shimada N, Ishikawa T, Tachi Y, Tada T, Toyoda H, Nouso K, Joko K, Hiasa Y, Michitaka K and Kudo M: Validation of modified ALBI grade for more detailed assessment of hepatic function in hepatocellular carcinoma patients: A multicenter analysis. Liver Cancer *8(2)*: 121-129, 2019. PMID: 31019902. DOI: 10.1159/000488778

13 Hiraoka A, Kumada T, Kudo M, Hirooka M, Tsuji K, Itobayashi E, Kariyama K, Ishikawa T, Tajiri K, Ochi H, Tada T, Toyoda H, Nouso K, Joko K, Kawasaki H, Hiasa Y, Michitaka K and Real-Life Practice Experts for HCC (RELPEC) Study Group and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics).: Albumin-Bilirubin (ALBI) grade as part of the evidence-based clinical practice guideline for HCC of the Japan Society of Hepatology: A comparison with the liver damage and child-pugh classifications. Liver Cancer *6(3)*: 204-215, 2017. PMID: 28626732. DOI: 10.1159/000452846

14 Hiraoka A, Michitaka K, Kumada T, Izumi N, Kadoya M, Kokudo N, Kubo S, Matsuyama Y, Nakashima O, Sakamoto M, Takayama T, Kokudo T, Kashiwabara K and Kudo M: Validation and potential of albumin-bilirubin grade and prognostication in a nationwide survey of 46,681 hepatocellular carcinoma patients in Japan: The Need for a more detailed evaluation of hepatic function. Liver Cancer *6(4)*: 325-336, 2017. PMID: 29234636. DOI: 10.1159/000479984

15 Terashima T, Yamashita T, Takata N, Toyama T, Shimakami T, Takatori H, Arai K, Kawaguchi K, Kitamura K, Yamashita T, Sakai Y, Mizukoshi E, Honda M and Kaneko S: Comparative analysis of liver functional reserve during lenvatinib and sorafenib for advanced hepatocellular carcinoma. Hepatol Res *50(7)*: 871-884, 2020. PMID: 32307874. DOI: 10.1111/hepr.13505

16 Sasaki R, Fukushima M, Haraguchi M, Miuma S, Miyaaki H, Hidaka M, Eguchi S, Matsuo S, Tajima K, Matsuzaki T, Hashimoto S, Ooba K, Kugiyama Y, Yatsuhashi H, Motoyoshi Y, Shigeno M, Kinoshita N and Nakao K: Response to lenvatinib is associated with optimal relativedose intensity in hepatocellular carcinoma: Experience in clinical settings. Cancers (Basel) *11(11)*: 2019. PMID: 31717674. DOI: 10.3390/cancers11111769

17 Kirino S, Tsuchiya K, Kurosaki M, Kaneko S, Inada K, Yamashita K, Osawa L, Hayakawa Y, Sekiguchi S, Okada M,

Wang W, Higuchi M, Takaura K, Maeyashiki C, Tamaki N, Yasui Y, Nakanishi H, Itakura J, Takahashi Y, Asahina Y and Izumi N: Relative dose intensity over the first four weeks of lenvatinib therapy is a factor of favorable response and overall survival in patients with unresectable hepatocellular carcinoma. PLoS One *15(4)*: e0231828, 2020. PMID: 32310967. DOI: 10.1371/journal.pone.0231828

18 Takahashi A, Moriguchi M, Seko Y, Ishikawa H, Yo T, Kimura H, Fujii H, Shima T, Mitsumoto Y, Ishiba H, Takashima H, Nagao Y, Jo M, Arai M, Hara T, Okajima A, Muramatsu A, Morita A, Yoshinami N, Nakajima T, Mitsuyoshi H, Umemura A, Nishikawa T, Yamaguchi K and Itoh Y: Impact of relative dose intensity of early-phase lenvatinib treatment on therapeutic response in hepatocellular carcinoma. Anticancer Res *39(9)*: 5149-5156, 2019. PMID: 31519627. DOI: 10.21873/anticanres.13710

19 Uojima H, Chuma M, Tanaka Y, Hidaka H, Nakazawa T, Iwabuchi S, Kobayashi S, Hattori N, Ogushi K, Morimoto M, Kagawa T, Tanaka K, Kako M and Koizumi W: skeletal muscle mass influences tolerability and prognosis in hepatocellular carcinoma patients treated with lenvatinib. Liver Cancer *9(2)*: 193-206, 2020. PMID: 32399433. DOI: 10.1159/000504604

20 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL and IMbrave150 Investigators.: Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med *382(20)*: 1894-1905, 2020. PMID: 32402160. DOI: 10.1056/NEJMoa1915745

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