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Original Article

Clinical Significance of Sarcopenia in Patients with Advanced Hepatocellular Carcinoma Undergoing Sorafenib Treatment

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ABSTRACT

Purpose: Sarcopenia has been associated with poor outcomes in patients with cirrhosis and solid tumors. However, information is limited on the prevalence and significance of sarcopenia in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib. In the present study, we investigated the prognostic value of sarcopenia in patients with advanced HCC, treated with sorafenib after stratification by standard prognostic factors.

Materials and Methods: We enrolled 85 patients (77 males and 8 females) treated with sorafenib from August 2007 to August 2016. The bilateral psoas muscle area at the L3 vertebral level was measured from computed tomography images, just before sorafenib administration. This area was normalized by patients' height, using units described in mm^2/m^2. Patients were classified into sarcopenia and non-sarcopenia groups using a cutoff value of 575.8 mm^2/m^2.

Results: The 3-year overall survival rate was 22.4%. Univariate analysis revealed the presence of sarcopenia (P=0.001), a baseline alpha-fetoprotein level of ≥100 ng/ml (P=0.022), derived neutrophil-to-lymphocyte ratio (P=0.019), and platelet-to-lymphocyte ratio (P=0.003) to be independent prognostic factors. In multivariate analysis, sarcopenia was independently associated with reduced overall survival (P=0.043). However, sarcopenia was not associated with reduced time on treatment.

Conclusion: In sorafenib treatment for advanced HCC, sarcopenia may be a significant prognostic factor and is associated with reduced survival.

Keywords: Hepatocelluar carcinoma; Prognostic factor; Sarcopenia

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the major causes of cancer-related mortality in the world [1]. In Korea, HCC is the fifth most common cancer type in male and sixth in female [2]. HCC is known to affect the elderly predominantly and is often diagnosed in advanced stage [3,4]. Recently, there have been remarkable developments in treatment modalities for HCC. Sorafenib, a multi-kinase inhibitor suppressing cancer growth and cell proliferation, is one of the promising treatment options, which can be used in those not amenable to transcatheter arterial chemoembolization (TACE) or liver transplantation due to HCC with an advanced stage [5]. Sorafenib has been also recommended as first line therapy to treat HCC [6].

There have been a number of markers which can be used to predict the prognosis after treatment with sorafenib: metastasis, vascular invasion, tumor size and other blood markers [7]. Recently, presence of sarcopenia before sorafenib administration has been suggested as another useful marker to predict the prognosis. Due to the absence of confirmed definition to evaluate the presence of sarcopenia, however,

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there have been contrasting results regarding the effect of sarcopenia on the treatment results of sorafenib [8,9]. In addition, there is no consensus on the definition of sarcopenia in Korean population [10], which led to the absence of studies investigating the association between sarcopenia and sorafenib in patients with HCC.

In the present study, we investigated the prognostic value of sarcopenia in patients with advanced HCC treated with sorafenib in a single tertiary center. Because of the absence of definition for sarcopenia in Korean population, we evaluated the presence of sarcopenia in the participating patients based on their median muscle mass.

MATERIALS AND METHODS

1. Patients and sorafenib therapy

This is a retrospective, single center study conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Kyung Hee University Hospital (KHUH 2021-07-017) and informed consent was waved. 85 patients (77 males and 8 females) treated with sorafenib at Kyung Hee University Hospital between August 2007 and August 2016 were included in this study. HCC was diagnosed according to the criteria of the American Association for the Study of Liver Disease [11] and its staging was based on abdominal dynamic contrast-enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging. All patients were diagnosed as advanced HCC having Barcelona Clinic Liver Cancer (BCLC) stage C or BCLC stage B which unfit to any or failed to respond to locoregional therapies. Sorafenib was used for patients with unresectable HCC and with following features such as the presence of distant metastasis, vascular invasion, tumor thrombus in the portal vein, and refractory response to or unsuitability for TACE, transcatheter arterial infusion (TAI) chemotherapy [12,13]. The initial dose of sorafenib was 800 mg/day for patients with no evident risk factors, but was reduced to 400 mg/day in those with old age, low body weight, high risk of bleeding, Child-Pugh grade B, or pleural effusion/ascites [14-16], which was determined by the physician's decision. Sorafenib therapy was discontinued in cases of radiologic or symptomatic progression of HCC, unacceptable sorafenib-associated toxicity or patients' wish to discontinue the therapy. Tumor progression was evaluated according to the modified Response Evaluation Criteria in Solid Tumors [17,18] and/or clinically based on the presence of worsened performance status or symptoms unrelated to liver failure. In case of discontinuation, possibility of performing other therapies such as TACE, TAI or chemotherapy other than sorafenib was considered by physicians.

2. Definition of sarcopenia

In order to assess the presence of sarcopenia in enrolled patients, this study utilized the CT scan data obtained 1 month prior to sorafenib administration. The skeletal muscle index (SMI) was calculated by summing cross-sectional area of bilateral psoas muscle at the level of third lumbar vertebra (measured by a hepatologist after manual tracing on the CT images) and normalizing it by the square of patients' height [19]. All CT images were analyzed by one observer, and the tissue Hounsfield unit (HU) limit for the skeletal muscle on CT images was between –29 HU to +150 HU [20]. Patients were classified into either sarcopenia or non-sarcopenia group using a cutoff value of 575.8 mm^2/m^2 which is the median value of SMIs of all enrolled patients in our study (Table 1).

3. Statistical analysis

Patients were classified into two groups according to the presence of sarcopenia based on the cutoff value described above and baseline characteristics of two groups were compared, expressed as mean±standard deviation or median. Student's t-test or Mann-Whitney test was performed for group comparison. Categorical variables were described as number (percentage) and compared by using the χ^2 test with Fisher's exact test. Overall survival (OS) was calculated from the initiation date of sorafenib administration until death due

Table 1. Backgrounds of patients treated with sorafenib

Variable	Value
Age (yr)	60.7 (33~85)
Male	77 (90.6)
Etiology	
Alcohol	10 (11.8)
HBV	56 (65.9)
HCV	9 (10.6)
Others	10 (11.8)
BMI (kg/m^2)	24.2±3.4
Albumin (g/dL)	3.7±0.4
Total bilirubin (mg/dL)	1.2±1.0
Prothrombin time	1.1±0.1
AFP	9,175.8 (1.4~60,500.0)
PIVKA-II	11,968.5 (11~75,000.0)
Child-Pugh grade A	79 (92.9)
Tumor vascular invasion (+)	40 (47.1)
Extrahepatic metastasis	49 (57.6)
BCLC stage B	29 (34.1)
BCLC stage C	56 (65.9)
L3 SMI (mm^2/m^2)	575.8 (214.3~1,107.0)

Values are presented as median (range), number (%), or mean±standard deviation.
AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; BMI = body mass index; HBV = hepatits B virus; HCV = hepatitis C virus; PIVKA-II = prothrombin induced by vitamin K absence or antagonist-II; SMI = skeletal muscle index.

to any cause or until the last follow up by using Kaplan-Meier curves and differences in the curves were assessed by the log-rank test. A Cox proportional hazards model was used for univariate analyses to determine significant factors associated with OS. The significant variables in univariate analyses were entered in multivariate analyses to find out the significant risk factors for OS in HCC patients treated with sorafenib. All statistical analyses were performed with SPSS (version 23.0; IBM Corp., Armonk, NY, USA), and a P-value<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of enrolled patients are shown in Table 1. Their median age was 60.7 (33~85) years and 77 (90.6%) of them were male. 56 patients (65.9%) had hepatitis B virus-related etiology for HCC. Baseline liver function was Child-Pugh grade A in 79 patients (92.9%) and median albumin level was 3.7±0.4 g/dL. The average duration of sorafenib administration was 3 months.

As described previously, since the enrolled patients were classified according to the median value of SMI (575.8 mm^2/m^2 [214.3~1,107.0]), the equal number of patients were included in either sarcopenic or non-sarcopenic group, and obviously SMI of two groups were significantly different (430.1±91.6 for sarcopenic group vs. 738.7±132.1 for non-sarcopenic group; P<0.001) (Table 2). Compared with those in non-sarcopenic group, age, sex and etiology of HCC in sarcopenic group were not significantly different, but higher body mass index (BMI) in non-sarcopenic group was observed. Laboratory analysis revealed that albumin, alpha-fetoprotein (AFP), neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR) and prognostic nutritional index were significantly different between two groups (Table 2).

The median follow-up periods subsequent to sorafenib administration were 6.4 months for sarcopenic group and 20.6 months for non-sarcopenic group. The 3-year OS rate was 22.4%. The OS curve between two groups is shown in Fig. 1. The overall curve for sorafenib treatment duration between two groups is shown in Fig. 2. According to the univariate

Table 2. Comparison of clinical and biochemical characteristics among sarcopenic and non-sarcopenic patients

Variable	Sarcopenic	Non-sarcopenic	P-value
L3 SMI	430.1±91.6	738.7±132.1	0.001
Age (yr)	62.6±11.6	59.0±10.4	0.143
Male	36 (85.7)	41 (95.3)	0.128
Etiology			
Alcohol consumption	6 (14.3)	4 (9.3)	0.853
HBV	26 (61.9)	30 (69.8)	-
HCV	5 (11.9)	4 (9.3)	-
Others	5 (11.9)	5 (11.6)	-
BMI (kg/m^2)	23.0±3.4	25.5±3.0	0.001
Albumin (g/dL)	3.5±0.4	3.8±0.4	0.024
Total bilirubin (mg/dL)	1.0±0.7	1.4±1.2	0.158
Prothrombin time	1.1±0.1	1.1±0.1	0.423
AFP	14,105.8 (2.4~60,500.0)	4,435.0 (1.4~60,500.0)	0.011
PIVKA-II	17,193.9 (13.0~75,000.0)	7,720.3 (11.0~75,000.0)	0.094
Tumor vascular invasion	21 (50.0)	19 (44.2)	0.591
Extrahepatic metastasis	25 (59.5)	24 (55.8)	0.729
BCLC stage C	28 (66.7)	28 (65.1)	0.880
NLR	5.1±4.3	3.4±2.4	0.034
dNLR	3.0±2.3	2.0±1.2	0.023
PLR	197.7±145.4	149.6±130.8	0.114
ALBI	2.0±2.1	2.4±1.4	0.408
PNI	35.9±4.5	38.1±4.5	0.026

Values are presented as median (range), number (%), or mean±standard deviation.
- = not available; AFP = alpha-fetoprotein; ALBI = albumin-bilirubin score; BCLC = Barcelona Clinic Liver Cancer; BMI = body mass index; dNLR = derived neutrophil-to-lymphocyte ratio; HBV = hepatitis B virus; HCV = hepatitis C virus; NLR = neutrophil-to-lymphocyte ratio; PIVKA-II = prothrombin induced by vitamin K absence or antagonist-II; PLR = platelet-to-lymphocyte ratio; PNI = Prognostic nutritional index; SMI = skeletal muscle index.

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analysis, the independent prognostic factors associated with OS were the presence of sarcopenia (P=0.001), a baseline AFP level of ≥100 ng/mL (P=0.022), dNLR (P=0.019), and PLR (P=0.003) (Table 3). Multivariate analysis revealed that sarcopenia was the only factor independently associated with reduced OS (P=0.043), however, it was not associated with reduced time on treatment (P=0.246).

DISCUSSION

The present study was designed to investigate the usefulness of sarcopenia as a prognostic factor in patients with advanced HCC treated with sorafenib after stratification by standard prognostic factors. The 3-year OS rate was 22.4%, and it was found out that the presence of sarcopenia, a baseline AFP level (≥100 ng/mL), dNLR, and PNR were significant prognostic factors for patients with HCC enrolled in this study. Sarcopenia remained to be significant after the multivariate analysis, leading to the conclusion that sarcopenia has an independent association with reduced OS in patients with HCC receiving sorafenib therapy. However, sarcopenia was not associated with reduced time on treatment.

Previous studies have reported that the reduction of muscle mass in patients with HCC has a significant effect on the

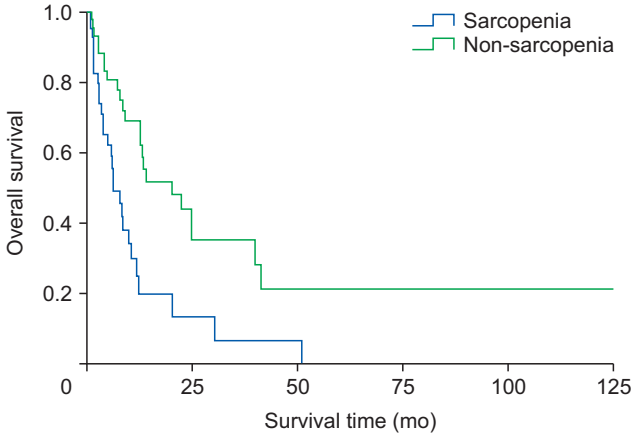

Fig. 1. Kaplan–Meier curve for overall survival comparing sarcopenic and non-sarcopenic patients.

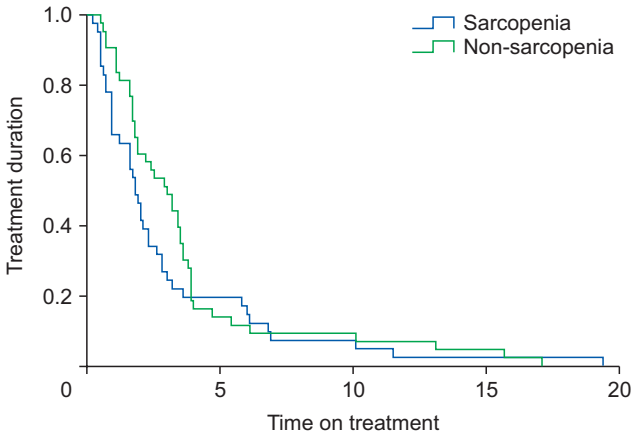

Fig. 2. Kaplan–Meier curve for sorafenib treatment duration comparing sarcopenic and non-sarcopenic patients.

Table 3. Univariate and multivariate analysis of risk factors for overall survival of hepatocellular carcinoma patients treated with sorafenib by the Cox proportional hazards model

Variable	Univariate			Multivariate		
	P-value	HR	95% CI	P-value	HR	95% CI
Age (<65 yr)	0.724	1.110	0.621~1.982	-	-	-
Sex	0.992	0.994	0.306~3.230	-	-	-
BMI (<25 kg/m^2)	0.144	1.547	0.855~2.796	-	-	-
Albumin (<3.2 g/dL)	0.709	1.154	0.542~2.460	-	-	-
AFP (≥100 ng/mL)	0.022	1.960	1.096~3.507	0.105	1.648	0.901~3.015
PIVKA-II (≥40 mAU/mL)	0.876	1.060	0.511~2.197	-	-	-
Tumor vascular invasion	0.448	1.239	0.709~2.164	-	-	-
Extrahepatic metastasis	0.173	0.684	0.394~1.188	-	-	-
NLR (≥3.2)	0.097	1.588	0.913~2.764	-	-	-
dNLR (≥2.0)	0.019	1.927	1.102~3.371	0.710	1.131	0.590~2.167
PLR (≥127.4)	0.003	2.309	1.301~4.097	0.238	1.498	0.766~2.932
ALBI (≥2.8)	0.296	0.747	0.430~1.297	-	-	-
PNI (≥38)	0.807	0.933	0.533~1.634	-	-	-
Sarcopenia	0.001	2.606	1.471~4.616	0.043	1.952	1.021~3.733

AFP = alpha-fetoprotein; ALBI = albumin-bilirubin score; BMI = body mass index; CI = confidence interval; dNLR = derived neutrophil-to-lymphocyte ratio; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; PIVKA II = protein induced by vitamin K absence or antagonists II; PLR = platelet-to-lymphocyte ratio; PNI = Prognostic nutritional index.

prognosis of these patients [21,22]. Also, the prognosis was reported to be different according to the baseline muscle mass in patients with HCC when treated with sorafenib [8]. Therefore, it is imperative to understand the useful factors to predict the treatment effect when using sorafenib in HCC.

As described previously, there have been diverse results regarding the effect of sarcopenia in treating HCC with sorafenib. Besides the studies which demonstrated the usefulness of sarcopenia to predict the prognosis of patients treated with sorafenib [8,23], other study reported that the predictive power of sorafenib was only limited in those showing less than two negative prognostic factors [7]. In addition, it was reported that sarcopenia only in those showing the reduction of mass during the treatment played a significant role as a predictive marker for future prognosis [24].

These inconsistent data seem to be possibly due to the difference of the methods to evaluate the sarcopenia. Yamashita et al. [24] directly measured the psoas muscle thickness to evaluate sarcopenia, while other studies used a software to measure the whole muscle mass at the L3 vertebra level [7,9]. Hiraoka et al. [8] measured the whole muscle mass at the L3 vertebra level by manual calculation without using a software, which was applied in our study and two studies produced similar results. Besides the difference in measuring methods, the definition of sarcopenia varied according to the race, nation or society [25,26]. Our study measured the muscle mass as described by Hiraoka et al. [8], but defined the presence of sarcopenia based on the median muscle mass of all participating patients, unlike other studies which applied certain cutoff values. Derstine et al. [27] defined sarcopenia as 45.4 cm^2/m^2 for males and 34.4 cm^2/m^2 for females on L3 vertebra level muscle volume in American populations. In the Korean population, Sarcopenia was defined as a L3 SMI of ≤49 cm^2/m^2 for males and ≤31 cm^2/m^2 for females using Korean-specific cutoffs [28]. However, as in the paper published by Ishii et al. [29], the median value was used to analyze the relationship between sarcopenia and patient prognosis in this study.

For the same reason, it is not easy to find out the exact prevalence of sarcopenia in Korea, but the prevalence of sarcopenia is higher in old population in Korea [30]. Since the prevalence of sarcopenia in cancer patients is higher than general population [31] and the diagnosis of HCC at an old age is increasing [2], it is expected that the number of HCC patients accompanying sarcopenia is likely to also increase, leading to the further clinical importance of sarcopenia in those treated with sorafenib.

Unlike previous studies, BMI was significantly different according to the presence or absence of sarcopenia. Also, neither extrahepatic metastasis nor vascular invasion did not demonstrate the significant effect on the prognosis. These differences may be possibly due to the different cut-off value applied for determining the presence of sarcopenia. There are some limitations in this study; our study was based on a retrospective design and did not investigate the association between the use of sorafenib and its adverse events. Median value of psoas muscle area was used as the cutoff value of sarcopenia, potentially creating bias. Also, the presence of sarcopenia was determined by manual calculation of muscle mass at the L3 vertebra level unlike previous studies [7,9] which used a measuring software. However, manual calculation of muscle mass was also verified by previous studies [8,32], and our calculation encompassed all the muscles shown in the transverse image selected for maximizing the opportunity to collect a representative muscle mass sample, which is believed not to affect the sensitivity of analysis in our study.

CONCLUSION

Sarcopenia was identified to have an independent association with reduced OS in patients with HCC receiving sorafenib therapy in Korea. Further study with larger cohort is necessary to confirm the result and compensate the limitation of this study in the future.

AUTHOR CONTRIBUTIONS

Conceptualization: MSP. Data curation: MSP, MHL. Formal analysis: MSP, MHL. Funding acquisition: MSP. Investigation: MSP. Methodology: MSP. Project administration: MSP. Resources: MSP. Software: MSP. Supervision: MSP. Validation: MSP. Visualization: MSP. Writing – original draft: MSP, MHL. Writing – review & editing: MSP.

CONFLICTS OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

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