Liver Cancer

Liver Cancer 2020;9:148–155
DOI: 10.1159/000503829
Received: June 21, 2019
Accepted: September 11, 2019
Published online: November 8, 2019

Original Paper

Skeletal Muscle Loss during Tyrosine Kinase Inhibitor Treatment for Advanced Hepatocellular Carcinoma Patients

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Keywords
Skeletal muscle · Hepatocellular carcinoma · Tyrosine kinase inhibitor · Sorafenib · Lenvatinib

Abstract
Introduction: The measurement of body composition such as the skeletal muscle index (SMI) has been reported to be useful for predicting prognosis in hepatocellular carcinoma (HCC). In this study, we analyzed skeletal muscle change during sorafenib and lenvatinib therapy and the association between SMI and prognosis. ***Methods:*** A total of 67 patients with advanced HCC and Child-Pugh grade A status treated with tyrosine kinase inhibitors (TKIs) at Hiroshima University between September 2009 and December 2018 were enrolled in this retrospective cohort study. Patients underwent computed tomography (CT) imaging before starting sorafenib treatment and 1–3 months after treatment initiation. ***Results:*** In all patients, the median SMI was 45.3 cm^2/m^2 before TKI treatment and 42.1 cm^2/m^2 after treatment; 54 of 67 (80.6%) patients experienced SMI loss. The median ΔSMI was –1.5 cm^2/m^2/months, and no difference in ΔSMI was observed between patients receiving sorafenib and lenvatinib. No significant differences were observed in median ΔSMI between patients with and without progressive disease (–2.35 and –1.1 cm^2/m^2/months, respectively), albumin-bilirubin grade 1 and 2 group disease (–1.7 and –1.5 cm^2/m^2/months, respectively), and relative dose intensity ≤80 and >80 (–1.8 and –1.2 cm^2/m^2/months, respectively). ***Conclusion:*** This report demonstrated that patients receiving TKI treatment experienced a significant loss of skeletal muscle mass regardless of disease progression, hepatic reserve, or which TKI (sorafenib or lenvatinib) they received.

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide [1]. HCC commonly occurs in patients with chronic hepatitis or liver cirrhosis due to hepatitis B virus (HBV) or hepatitis C virus (HBC), alcohol use, nonalcoholic steatohepatitis, or diabetes [2].

Tyrosine kinase inhibitors (TKIs) are currently the standard of care for the systemic treatment of patients with advanced HCC who are not candidates for potential curative options, such as surgical resection, transplantation, or locoregional therapy. Sorafenib and lenvatinib inhibit tumor cell proliferation and tumor angiogenesis-driven cancer growth [3–5].

Previous studies on prognostic factors in patients with HCC who underwent sorafenib therapy have been focused on tumor-associated factors, such as hepatic reserve, serum biomarkers, and combination therapy [6–8]. Interestingly, the measurement of body composition, such as skeletal muscle index (SMI), has also been reported to be useful for predicting prognosis [9–14]. Computed tomography (CT) is used to evaluate skeletal muscle volume.

In this retrospective study, we analyzed skeletal muscle change during sorafenib and lenvatinib therapy and the association between SMI and prognosis.

Materials and Methods

Patients

A total of 67 patients with advanced HCC and Child-Pugh grade A status who initiated sorafenib or lenvatinib as the first-line TKI therapy at Hiroshima University between September 2009 and December 2018 were enrolled in this retrospective cohort study. Patients underwent CT imaging prior to and 1–3 months or longer after treatment initiation.

Treatment

Patients received 400 mg sorafenib twice daily or 8 mg/12 mg lenvatinib once daily based on their body weight. Treatment interruptions and dose reductions were permitted for adverse drug reactions. Treatment continued until death or until one of the following criteria were met: (i) adverse events that required termination of treatment; (ii) deterioration of Eastern Cooperative Oncology Group performance status (ECOG-PS); (iii) worsening liver function; (iv) withdrawal of consent. In our hospital, patients continued sorafenib and lenvatinib after the onset of radiological progressive disease (PD) as defined by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) when no definitive treatment exists for second-line therapy. Criteria for treatment discontinuation after PD were severe adverse effects leading to discontinuation, symptomatic progression, deterioration of hepatic reserve, deterioration of ECOG PS, and death.

Assessment of Skeletal Muscle

All patients underwent CT before TKI treatment and 1–3 months afterwards (or longer). The skeletal muscle area was measured from CT images. Using sliceOmatic software v5.0 (Tomovision, Montreal, QC, Canada), cross-sectional CT images were analyzed at the level of the third lumbar vertebra (L3) to determine skeletal muscle area. Skeletal muscle was identified and quantified by thresholds of –29 to +150 Hounsfield units (HU) [15]. Skeletal muscle mass was normalized for height in m^2 and expressed as the SMI in cm^2/m^2. Using SMI values, muscle depletion was defined as <42 cm^2/m^2 in men and <38 cm^2/m^2 in women, according to the Japan Society of Hepatology criteria [16]. Estimated SMI change during TKI therapy was based on the ΔSMI: (post SMI – pre SMI)/months from initiation to evaluation.

Evaluation of Response to Sorafenib and Lenvatinib

Radiological response was evaluated by CT 1–3 months or longer after sorafenib and lenvatinib initiation using mRECIST. Adverse drug reactions were defined according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE 4.0).

Table 1. Patients' pretreatment characteristics

	All (*n* = 67)	Sorafenib (*n* = 49)	Lenvatinib (*n* = 18)	*p* value
Age, years	70 (20–87)	68.0 (20–87)	71.5 (46–83)	0.213
Gender, M/F	56/11	41/8	15/3	1
Etiology, HBV/HCV/NBNC/HBV + HCV	16/28/22/1	14/21/13/1	2/7/9/0	0.233
Prothrombin activity, %	85 (45.0–106)	89.0 (45.0–106)	84.5 (63.5–99)	0.295
Serum albumin, g/dL	3.9 (2.9–4.8)	3.9 (3.1–4.8)	3.6 (2.9–4.8)	0.098
Serum total bilirubin, mg/dL	0.8 (0.4–1.7)	0.8 (0.4–1.7)	0.8 (0.4–1.7)	0.775
Child-Pugh score 5/6	44/23	35/14	9/9	0.147
Serum alpha fetoprotein, ng/mL	46 (0.5–2,650,000)	46.0 (1.2–2,650,000)	52.3 (0.5–121,590)	0.921
Serum des-γ-carboxy prothrombin, mAU/mL	475 (0.5–344,570)	475 (0.5–344,570)	635 (14.0–108,390)	0.651
T stage[a] 0/1/2/3/4	12/3/16/23/13	10/3/7/20/9	2/0/9/3/4	0.49
Extra hepatic metastasis absent/present	26/41	16/33	10/8	0.1
Size of hepatic tumor, mm	23 (0–180)	26.6 (0–180)	19.5 (0–120)	0.599
Tumor size relative to the liver, ≤50%/>50%	57/10	40/9	17/1	0.267
No. of hepatic tumors, ≤3/≥4	36/31	29/20	7/11	0.173
MVI absent/present	47/20	34/15	13/5	1
L3-SMI, cm^2/m^2	45.3 (26.6–62.0)	44.6 (26.6–62.0)	45.7 (37.3–61.4)	0.876
Muscle depletion absent/present	49/18	35/14	14/4	0.76

Data are expressed as median (range) or *n*. HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-hepatitis B virus and non-hepatitis C virus; MVI, macroscopic vascular invasion. [a] Based on the following 3 conditions (T factor): solitary, <2 cm in diameter, and no vessel invasion. T1 was defined as fulfilling all 3 conditions, T2 as fulfilling 2 of the conditions, T3 as fulfilling 1 of the conditions, and T4 as fulfilling none of the conditions.

Statistical Analysis

Univariate analysis was performed by log-rank test, using Fisher's exact test, the χ^2 test, or the Mann-Whitney U test. The Wilcoxon rank sum test was used to compare differences in SMI before and after treatment. Multivariate analysis of prognostic factors was performed by Cox proportional hazards regression. Variables were identified as being significant if they had *p* values <0.05 on univariate analysis. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for *R* (The *R* Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of *R* commander designed to add the statistical functions frequently used in biostatistics. Both overall survival (OS) and change of skeletal muscle mass during TKI treatment were assessed.

Results

Patients' Background Characteristics

Patients' characteristics and clinical data at TKI initiation are summarized in Table 1. The median patient age was 70 (range 20–87) years and 56/67 patients (83.6%) were male. Of all 67 patients, 16 (23.9%) were HBV antigen-positive, and 28 (41.8%) were HCV antibody-positive. Twenty patients (29.9%) had macroscopic vascular invasion (MVI) and 41 (61.2%) had extrahepatic metastasis. The median L3 SMI (L3-SMI) was 45.3 (range, 26.6–62.0) cm^2/m^2.

Assessment of the Response to TKI Treatment

Based on mRECIST, the number of patients with PD and non-PD was 22 (sorafenib, 18; lenvatinib, 4) and 45 (sorafenib, 31; lenvatinib, 14), respectively, at the evaluation at 1–3 months. Figure 1 shows the median survival time (MST) for all patients (15.6 months),

Table 2. Univariate and multivariate analysis of prognostic factors

	Univariate analysis[a]	Multivariate analysis[b]	95% CI	HR
Age, years (≤70 vs. >70)	0.112			
Gender (male vs. female)	0.731			
Etiology (viral vs. NBNC)	0.678			
Prothrombin activity, % (≤85 vs. >85)	0.655			
Serum albumin, g/dL (≤3.9 vs. >3.9)	0.331			
Serum total bilirubin, mg/dL (≤0.8 vs. >0.8)	0.546			
Child-Pugh score (5 vs. 6)	0.639			
ALBI grade (1 vs. 2)	0.811			
Serum α-fetoprotein, ng/mL (≤46 vs. >46)	0.113			
Serum des-γ-carboxy prothrombin, mAU/mL (≤475 vs. 475)	<0.001	0.993	1.000–1.000	1.0
Extrahepatic metastasis (absent/present)	0.498			
Tumor size relative to the liver (≤50 vs. >50)	0.052			
Number of hepatic tumors (<4 vs. ≥4)	0.026	0.286	0.7386–2.795	1.4
Macroscopic vascular invasion (absent vs. present)	<0.001	0.001	1.657–8.332	3.7
Muscle depletion (absent vs. present)	0.437			
Relative dose intensity (≤80 vs. >80)	0.333			
mRECIST (PD vs. non-PD at first evaluation)	0.122			

CI, confidence interval; HR, hazard ratio; NBNC, non-hepatitis B virus and non-hepatitis C virus; ALBI, albumin-bilirubin; mRECIST, modified Response Criteria in Solid Tumors; PD, progressive disease; non-PD, nonprogressive disease. [a] Log-rank test; [b] Cox proportional hazards regression.

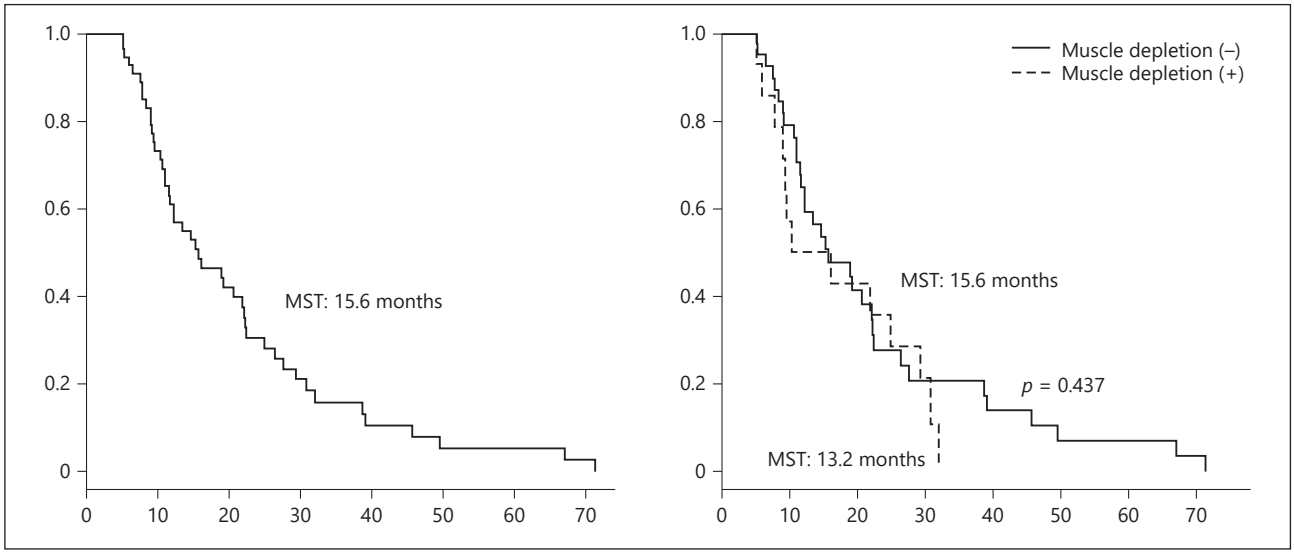

Fig. 1. Comparison of overall survival between patients with and without muscle depletion. MST, median survival time.

patients with muscle depletion (13.2 months), and patients without muscle depletion (15.6 months); the difference between these groups was not significant (p = 0.437). Prognostic factors identified on univariate analysis included low serum des-γ-carboxy prothrombin (DCP), a small number of hepatic tumors, and an absence of MVI. Multivariate analysis revealed only MVI as a prognostic factor (Table 2).

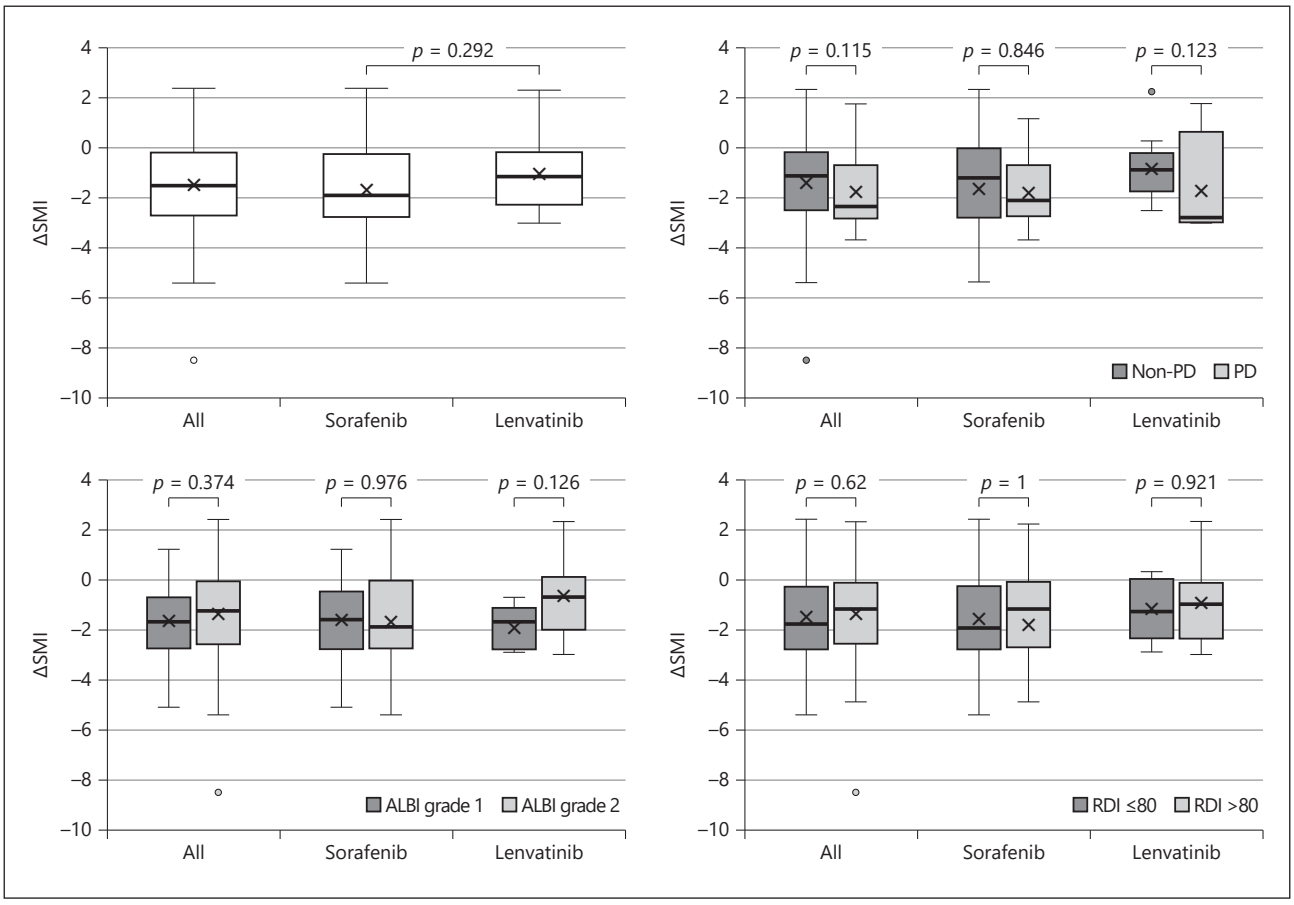

Fig. 2. Comparison of ΔSMI between sorafenib and lenvatinib. The Mann-Whitney U test was used.

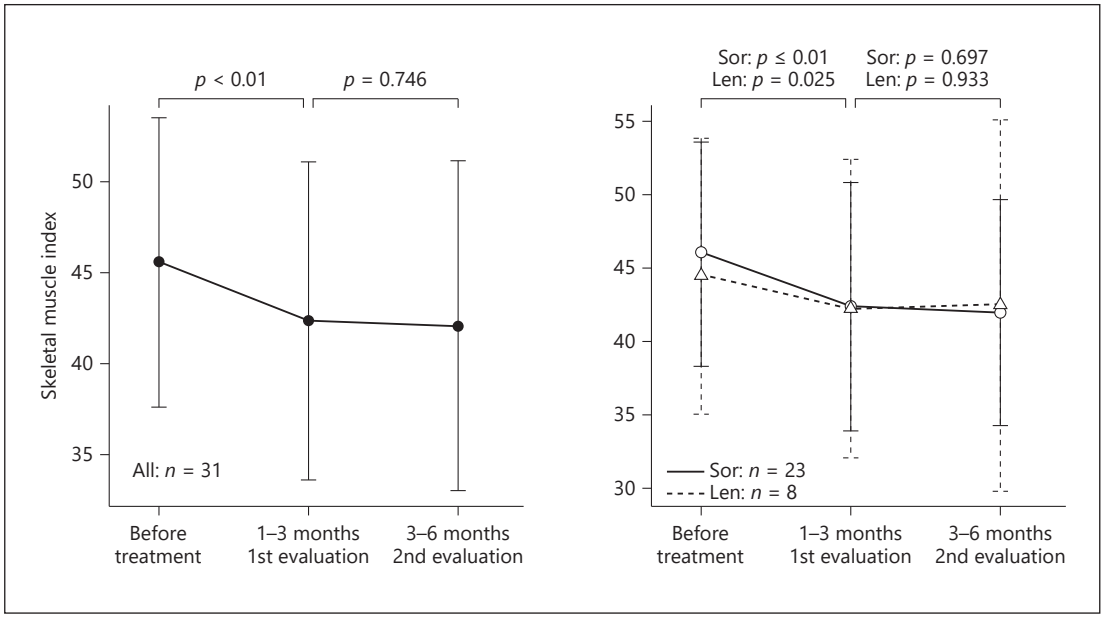

Fig. 3. Skeletal muscle change of patients was evaluated 3 times. Len, lenvatinib; Sor, sorafenib. The Wilcoxon rank sum test was used.

Skeletal Muscle Mass Changes in All Patients

Figure 2 shows the evaluation of ΔSMI during treatment. In all patients, the median SMI before TKI treatment was 45.3 cm^2/m^2 and afterwards it was 42.1 cm^2/m^2; 54/67 (80.6%) patients experienced a decrease in SMI.

Skeletal Muscle Mass Changes by Subgroup

The median ΔSMI was –1.5 cm^2/m^2/months, and no significant difference in ΔSMI was observed between the sorafenib and lenvatinib groups (p = 0.292). The median ΔSMI of patients with PD and non-PD was –2.35 and –1.1 cm^2/m^2/months, respectively (p = 0.115); between patients with albumin-bilirubin (ALBI) grade 1 and 2 disease it was –1.7 and –1.5 cm^2/m^2/months, respectively (p = 0.374); and between patients who received a relative dose intensity (RDI) of ≤80 and >80, it was –1.8 and –1.2 cm^2/m^2/months, respectively (p = 0.62). None of these differences was significant.

All patients showed a tendency to experience decreased skeletal muscle mass during TKI therapy. Figure 3 shows ΔSMI in 31 patients evaluated 3 times. A significant difference (p < 0.01) was observed between baseline and the first evaluation, but no significant difference (p = 0.746) was observed between the first and second evaluations. The result was similar in both the sorafenib and lenvatinib groups.

Discussion

In this study, we assessed the change of skeletal muscle mass in patients with HCC treated with TKIs. We used L3-SMI to evaluate the quantity of skeletal muscle and found that L3-SMI decreased in 54 of 67 patients treated with TKI therapy.

Several factors are associated with skeletal muscle depletion. In patients with cancer, reasons for skeletal muscle depletion include decreased physical activity and poor nutrition due to disease progression and the adverse effects of treatment, as well as increased expression of inflammatory cytokines [17]. In contrast, in patients with chronic liver disease, poor nutrition and loss of branch-chain amino acids (BCAAs) [18, 19] and carnitine [20] contribute to skeletal muscle loss.

The median ΔSMI of patients with PD and non-PD was –2.35 and –1.1, respectively. This suggests that patients treated with TKIs lose skeletal muscle regardless of tumor progression. When patients with ALBI grade 1 and 2 disease were compared, L3-SMI tended to decrease in both groups, and no difference in ΔSMI was observed. Moreover, L3-SMI decreased in patients who received sorafenib and in those who received lenvatinib. Previous reports have also demonstrated skeletal muscle loss in patients with renal-cell cancer [21] and lung cancer [22].

Sarcopenia is thought to be associated with alterations in the phosphoinositide PI3k/Akt/mTOR signaling pathway [23–26]. This pathway is associated with muscle protein synthesis. Since sorafenib and lenvatinib both inhibit VEGFR-mediated signaling and the carnitine transporter [27], this may lead to the suppression of downstream PI3k/Akt/mTOR pathway signaling and a subsequent skeletal muscle decrease.

We also assessed prognostic factors in this study. A previous report stated that muscle depletion was a prognostic factor for patients with HCC [9–14]. In our study, DCP, the number of intrahepatic tumors, and MVI were identified as prognostic factors in univariate analysis, while multivariate analysis revealed only MVI as a prognostic factor. Muscle depletion was not associated with prognosis; however, this needs to be assessed in more patients, and a high rate of MVI (29.9%) could also affect this result.

This report has some limitations, such as the small sample size, retrospective design, and short-term nature. We have shown that patients with TKI treatment significantly lost their

skeletal muscle mass regardless of disease progression, hepatic reserve, and TKI administration (either sorafenib or lenvatinib). From these results and those of previous reports [9–14], we should pay attention to muscle and nutrition during TKI therapy.

Statement of Ethics

This study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Hiroshima University (IRB No. 695). Written informed consent was obtained from each patient after a detailed explanation of the study procedure.

Disclosure Statement

The authors declare that they have no conflict of interest.

Funding Sources

This work received no funding support.

Author Contributions

S. Uchikawa and T. Kawaoka designed the study, analyzed the data, and wrote the paper; S. Uchikawa acquired the data and performed the statistical analysis; T. Kawaoka and H. Aikata reviewed the results; H. Aikata revised the manuscript for important intellectual content.

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