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Minimal impact of lenvatinib (Lenvima®) on muscle mass in advanced hepatocellular carcinoma and implications for treatment duration. Two cases from the REFLECT study

E. RINNINELLA[1,2], M. CINTONI[3], P. RAOUL[2], M.C. MELE[1,2], A.M. DE GAETANO[4,5], M.G. MARINI[6], V. MORA[7], A. GASBARRINI[2,7]

[1]UOSA Nutrizione Avanzata in Oncologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[2]Istituto di Patologia Speciale Medica, Università Cattolica del Sacro Cuore, Rome, Italy
[3]Scuola di Specializzazione in Scienza dell'Alimentazione, Università di Roma Tor Vergata, Rome, Italy
[4]UOC Radiologia Diagnostica e Interventistica Generale, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[5]Istituto di Radiologia, Università Cattolica del Sacro Cuore, Rome, Italy
[6]Scuola di Specializzazione in Radiodiagnostica, Università Cattolica del Sacro Cuore, Rome, Italy
[7]UOC di Medicina Interna e Gastroenterologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Abstract. – OBJECTIVE: Two case reports of advanced unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (Lenvima®) are presented; the drug's effect on muscle loss and duration of treatment are discussed.

PATIENTS AND METHODS: Between November 2014 and December 2017, at the Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy, two male patients with advanced HCC enrolled in the lenvatinib arm of the REFLECT trial received the drug over 24 cycles (almost 2 years). We reviewed the clinical charts from baseline, when lenvatinib was started, through 24 months of treatment. The changes in the skeletal mass area (SMA), as assessed by computed tomography (CT) at the third lumbar level (L3), between baseline and month 24 into treatment were recorded.

RESULTS: Case 1: SMA decreased by 2.8 cm^2 between baseline and month 24 (134 cm^2 *vs.* 131.2 cm^2), with a muscle loss of 2.13%. Case 2: SMA decreased by 13 cm^2 between baseline and month 24 (133 cm^2 *vs.* 120 cm^2), with a muscle loss of 10.83%.

CONCLUSIONS: The disease remained stable for over 2.5 years in both patients. A minimal loss of muscle mass was noted at 24 months of treatment. The minimum effect on muscle loss may be correlated with the positive clinical response and the drug's low toxicity. Our findings may help to elucidate the effect of lenvatinib on muscle mass and inform the development of the targeted nutritional support for HCC patients.

Key Words:
Sarcopenia, Nutrition, Dose-limiting toxicity, Hepatocellular carcinoma, Lenvatinib, Sorafenib.

Introduction

Liver cancer is the sixth most commonly diagnosed cancer and the fourth cause of cancer death worldwide, with about 841,000 new cases recorded in 2018[1]. Hepatocellular carcinoma (HCC) accounts for 75-85% of liver cancer and is among the leading causes of cancer-related mortality[1]. HCC is often diagnosed at an advanced stage when symptoms have manifested, heralding poor prognosis[2]. Between 2009 and 2017 the only systemic therapy approved for the treatment of unresectable HCC was the anti-angiogenic multikinase inhibitor sorafenib. Sorafenib was approved on the basis of the results of two large, randomized controlled trials (SHARP and Asia-Pacific trials)[3,4] that showed significant improvement in overall survival (OS) and in time-to-progression (TTP) *vs.* placebo. However, the drug's efficacy was hampered by a high rate of major adverse events, such as diarrhea, hand-foot skin reaction (HFSR), fatigue, and weight loss. Recently, lenvatinib has been approved as first-line systemic therapy for the treatment of advanced HCC[5], based on the

Corresponding Author: Emanuele Rinninella, MD; e-mail: emanuele.rinninella@unicatt.it

results of the randomized, double-blind, multinational, phase 3 REFLECT trial[6]. Lenvatinib resulted not inferior to sorafenib for OS (13.6 *vs*. 12.3 months; hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.79-1.06). Moreover, compared to sorafenib, the trial showed that lenvatinib significantly improved several secondary endpoints, including higher objective response rate (ORR), longer progression-free survival (PFS), and TTP[6].

Lenvatinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) against vascular endothelial growth factor receptors 1-3 (VEGFRs 1-3), fibroblast growth factor receptors 1-4 (FGFRs 1-4), platelet-derived growth factor receptor α (PDGFR-α), and the rearranged during transfection (RET) and c-KIT proto-oncogenes, which are implicated in tumor angiogenesis and tumor growth and progression[7].

REFLECT trial reported longer duration of treatment and better tolerability in the patients receiving lenvatinib than in those treated with sorafenib. Delayed worsening in health-related quality of life (HR-QOL), role functioning, pain, diarrhea, nutrition, and body image was also reported[6]. Additionally, slightly less loss of body weight and physical activity were observed in the lenvatinib-treated than in the sorafenib-treated group[8]. The reasons for these findings are not fully understood and need to be elucidated.

Among the clinical prognostic markers for cancer disease, muscle mass loss has attracted increasing attention. Sarcopenia is a prognostic factor of mortality and tumor recurrence in HCC patients[9], especially in those undergoing sorafenib therapy[10]. Computed tomographic (CT) imaging at the third lumbar vertebra (L3) is considered the gold standard, non-invasive tool to assess muscle quantity/mass. Because CT measurement of muscle mass at L3 directly correlates with whole-body muscle mass, it is a strong predictor of mortality in cirrhotic and HCC patients[11,12]. Although strong evidence suggests a role for sorafenib in determining weight loss, muscle wasting, and sarcopenia during treatment[13], the correlations between lenvatinib and sarcopenia have not been established and well-designed studies are needed. In this context, the two case reports presented here may help to elucidate the role of lenvatinib in muscle loss in advanced unresectable HCC.

Patients and Methods

Between November 2014 and December 2017, five patients with advanced HCC, naïve to systemic treatments, were recruited for the REFLECT study in which our center, Fondazione Policlinico A. Gemelli IRCCS, Rome, participated[6]. Three patients received sorafenib (Nexavar®, Bayer, Germany) at a dosage of 800 mg/day (400 mg twice daily) and two patients received lenvatinib (Lenvima®, Eisai Co., Ltd., Tokyo, Japan) according to body weight (12 mg/day for weight ≥60 kg or 8 mg/day for weight <60 kg) in 28-day cycles, as per study protocol. The three patients enrolled in the sorafenib arm withdrew from the study within 3 months because of unmanageable toxicities or progressive disease, while the two patients in lenvatinib arm continued taking the drug for over 24 cycles (almost 2 years in all). We retrospectively reviewed the patients' clinical charts and extracted data from the start of lenvatinib therapy through the following 24 months. The patients underwent monthly evaluation of clinical symptoms, laboratory values, and changes in quality of life; CT was performed every 2 months to assess tumor response to treatment, according to the trial protocol[14]. Skeletal muscle area (SMA; cm^2) was measured based on CT findings. A single axial at slice vertebra L3 was selected from the scans acquired at baseline and at 24 months. Image analysis software (SliceOmatic v5.0, Tomovision, Montreal, Canada) was used to define SMA according to predefined validated boundaries based on the number of Hounsfield Units (HU) in a range from -29 to +150 HU. The changes in SMA between baseline and at 24 months of lenvatinib treatment were recorded.

Results

Case 1

A 61-year old Asian man with a history of hepatitis B virus (HBV) - related cirrhosis (treated with tenofovir) was newly diagnosed with advanced HCC classified according to the Barcelona Clinic Liver Disease system (BCLC stage C) and defined as a large (11 cm in diameter) nodular lesion in the right lobe, with a neoplastic thrombus extending from above the right hepatic vein into the inferior vena cava and the right atrium. Examinations revealed acceptable functional status (Eastern Cooperative Oncology Group [ECOG] Performance Status 1), well compensated cirrhosis (Child A5), and controlled arterial hypertension. The body weight was 62 kg at the baseline visit. During clinical evaluation in December 2014, he gave informed, written consent to participate in the

REFLECT trial and was randomized to the lenvatinib arm (dosage 12 mg/day; 3 pills/day). The clinical course was unremarkable. He complained of mild asthenia and loss of appetite, which was not clinically significant. At the 5th cycle, he reported a slight, painless thickening of the skin of both hands, classified as HFSR grade 1 according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0)[15]. The skin reaction resolved with 15 days of topical treatment with 15% urea-based cream, without discontinuation of lenvatinib. At the 28th cycle, the body weight was 58 kg. The drug dosage was not reduced. At the 33rd cycle, grade 1 diarrhea was managed with loperamide and probiotics. The blood pressure levels remained under control throughout treatment. On completion of the 34th cycle, CT documented disease progression and treatment was discontinued. The patient was withdrawn from the study as per protocol. He died 2 months later in September 2017.

The patient had undergone lenvatinib treatment for 2.7 years without disease progression or significant complaints. Quality of life was reportedly also satisfactory. The change in SMA, as measured at level L3 between baseline and 24 months, was 2.8 cm^2 (134 cm^2 *vs.* 131.2 cm^2), with a muscle loss of 2.13%. Figure 1 presents the changes in SMA at level L3.

Case 2

An 83-year old Caucasian man with cryptogenic cirrhosis and multinodular intermediate HCC (BCLC stage B) diagnosed in November 2014 had undergone locoregional treatment (TACE transarterial chemoembolization) twice without radiological response and developed a complication (liver abscess) at the second treatment. The functional status was acceptable (ECOG 1) and cirrhosis was well compensated (Child A5). At the baseline visit, the body weight was 58 kg; clinical evaluation indicated that he was eligible for participation in the REFLECT trial[6]. In May 2015, after giving written, informed consent, he was randomized to the lenvatinib arm (drug dosage 8 mg/day, 2 pills/day). At the 3rd cycle a slight, painful stomatitis (CTCAE grade 1) developed, which was managed with chlorobutanol-based mouthwash for 10 days, without discontinuation of lenvatinib therapy. The stomatitis recurred at cycles 11, 23, and 30. Of note, the patient reported the occurrence of stomatitis also before beginning lenvatinib treatment. At the 30th cycle, the patient complained of diarrhea (CTCAE grade 1), which was managed with probiotics. At

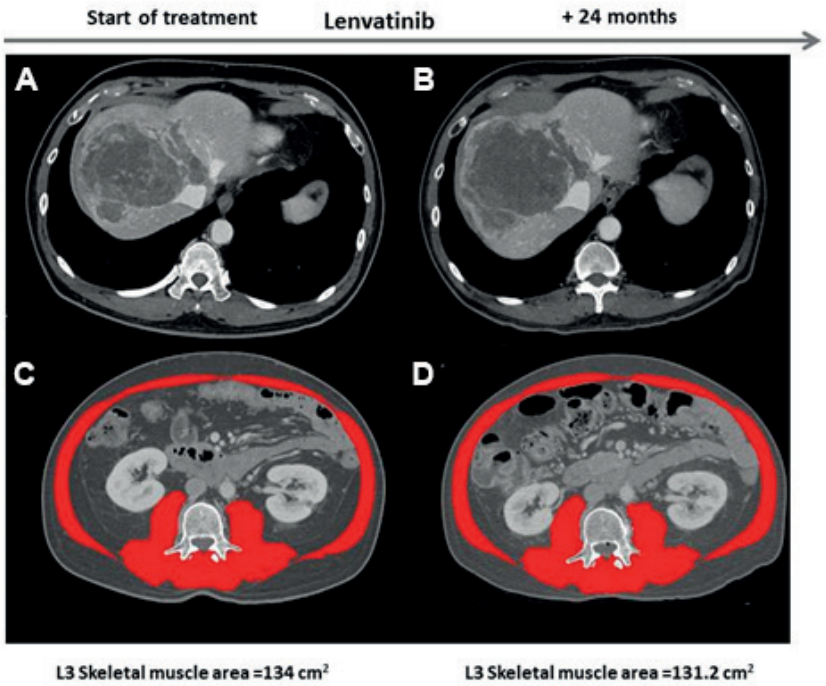

Figure 1. Skeletal muscle area (SMA) during chemotherapy with lenvatinib (Case 1). Panels A and B: CT scans of the liver at baseline (A) and at 24 months of chemotherapy (B), showing substantially stable disease. Panels C and D: CT scans of the skeletal muscle at the L3 level at baseline (C) and at 24 months of chemotherapy (D).

the 35th cycle, the body weight was 54.5 kg. Blood pressure values remained within the normal range. At the 37th cycle, severe fatigue (CTCAE grade 3) and joint pain (CTCAE grade 3) developed, which severely impaired walking. He discontinued lenvatinib treatment in May 2018 and withdrew from the study as per trial protocol. He died 6 months later in November 2018. At the off-treatment visit, the last CT scan showed stable disease. He had undergone lenvatinib treatment for 2.10 years, during which the disease remained stable and significant adverse events occurred after completion of 37 cycles of therapy. The quality of life was reported as acceptable until the end of treatment. The change in SMA at level L3 between baseline and 24 months after the start of treatment was 13 cm^2 (133 cm^2 *vs.* 120 cm^2), with a muscle loss of 10.83%. Figure 2 presents the changes in SMA at level L3.

Discussion

The two patients did not present significant skeletal muscle loss *vs.* baseline as measured by CT scans at 24 months of lenvatinib therapy. To date, only one multicenter analysis has quantified psoas muscle loss by CT in HCC patients treated with lenvatinib: a decline in total psoas muscle area was noted after 4 weeks of treatment (-0.210 ± 0.315 cm^2/m^2) in 41 patients and after 12 weeks of treatment (-0.275 ± 0.372 cm^2/m^2) in 25 patients[16]. However, according to the revised consensus of the European Working Group on Sarcopenia in Older People (EWGSOP)[17], the psoas is not considered representative of overall sarcopenia as it is a "minor muscle"; therefore, further studies are needed to determine the usefulness of psoas muscle thickness to diagnose sarcopenia. The present results are controversial and should be interpreted with caution, because of the small number of patients and the lack of comparison with control groups and/or treatment groups with other TKIs, such as sorafenib. Nonetheless, the following points merit discussion.

Severe skeletal muscle loss, a well-known marker of sarcopenia, is an important, independent prognostic factor in patients with solid tumors[18]. Sarcopenia as measured by CT has been identified as a risk factor for clinical outcomes, such as OS in various malignancies[19]. In HCC, sarcopenia develops in almost one-third of patients and constitutes a strong, independent risk factor for mortality[12], with increased risk of severe chemotherapy toxicity[20].

Muscle loss during chronic diseases, such as cancer is mainly attributed to alterations in

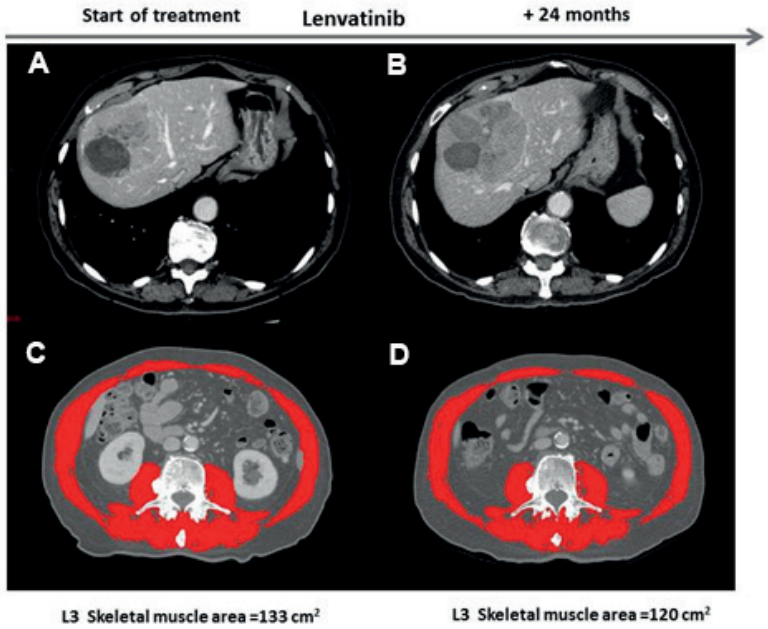

Figure 2. Skeletal muscle area (SMA) during chemotherapy with lenvatinib (Case 2). Panels A and B: CT scans of the liver at baseline **(A)** and at 24 months of chemotherapy **(B)** showing substantially stable disease. Panels C and D: CT scans of the skeletal muscle at the L3 level at baseline **(C)** and at 24 months of chemotherapy **(D)**.

protein metabolism caused by the tumor and by systemic inflammatory response[13]. The impact of sorafenib therapy on muscle loss has been demonstrated in advanced renal cell carcinoma[13]. Analysis of clinical and body composition data from CT scans of patients involved in a multicenter, blinded, placebo-controlled, randomized, phase 3 study (TARGET) evaluating sorafenib for the treatment of advanced renal cell carcinoma[21] showed that the muscle loss was exacerbated by sorafenib (*vs.* placebo). A significant muscle loss was seen in the first 6 months of sorafenib treatment and continued to progress until 12 months of observation. By the first full year of sorafenib treatment, patients had cumulatively lost 4.2 ± 0.7 kg of weight, 12.1 ± 1.5 cm^2 of total muscle area, and 33.1± 8.1 cm^2 of total adipose tissue area ($p<0.01$)[20]. A recent retrospective study by Antonelli et al[22] revealed that sarcopenia was present in almost half of cirrhotic HCC patients undergoing sorafenib therapy, with a two-fold higher risk of mortality and shorter treatment duration in sarcopenic patients. Similar findings confirm those of Takada et al[23] regarding OS, though the authors found no clear association between sarcopenia assessed before sorafenib administration and treatment cycle or dose reduction.

Sorafenib and lenvatinib are orally administered TKIs, with antiangiogenic activity *via* VEGFRs[13]. However, lenvatinib exerts dual inhibition of the VEGF and the FGF pathway, both factors in its anti-tumor effects[24]. One of the main mechanisms by which sorafenib inhibits tumor cell proliferation and survival is by downstream suppression of PI3K, AKT, and mTOR, which are the chief mediators in the activation of muscle protein synthesis by amino acids. The AKT/mTOR pathway is upregulated during hypertrophy and downregulated during muscle atrophy[13]. Although the molecular pathways involved in sarcopenia are not fully elucidated, the decrease in protein synthesis rate appears to be one of the most critical events. A preliminary report[25] highlighted the correlations between sarcopenia and mTOR pathways in patients with colorectal cancer. In light of these correlations, our preliminary results, and the fact that the mTOR pathway is implicated only in sorafenib molecular pathways, we hypothesize that its suppression is involved in causing muscle loss in sorafenib-treated patients.

Another difference between lenvatinib and sorafenib concerns drug dosage. The recommended sorafenib regimen is 400 mg twice daily[20], whereas the recommended lenvatinib dosage depends on the patient's body weight: 8 mg if <60 kg and 12 mg if ≥60 kg. An exposure-response relationship was observed between lenvatinib withdrawal and body weight, indicating that dose adjustment with optimal body weight cut-off values improves lenvatinib safety in the treatment of HCC patients[26]. We can further hypothesize that dosage adjustments for body weight could also improve the drug's tolerability and delay the metabolic effects of sarcopenia.

Finally, our patients received nutritional support according to international guidelines during lenvatinib therapy[27]. Early nutrition evaluation, assessment, and personalized nutritional support all have an effect on body composition, including skeletal muscle[28,29]. Randomized controlled studies with a large number of HCC patients are needed to assess the impact of nutritional support during lenvatinib treatment on sarcopenia.

Conclusions

We present the case reports of two patients treated with lenvatinib for HCC, in which the duration of therapy and disease stability were longer than has been reported in the literature to date. Due to the small number of patients, we cannot conclude whether lenvatinib might have less effect on muscle loss compared to sorafenib. Retrospective review of CT images at lumbar level L3 indicated a minimal loss of muscle mass after 24 months of therapy; this evidence could be potentially correlated with clinical response and low drug toxicity. The present results should be interpreted with caution. Nevertheless, they may offer useful information for evaluating the impact of lenvatinib on muscle mass. Targeted nutritional support during treatment is necessary to improve clinical outcomes, OS, and quality of life in HCC patients.

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Conflict of Interests

The Authors declare that they have no conflict of interests

Ethical Conduct of Research

This study was approved by the local Ethics Committee and was conducted in accordance to the tenets of the Declaration of Helsinki. Written, informed consent was obtained from the patients for the use of their clinical data.

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