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Body Composition and Leptin/Ghrelin Levels during Lenvatinib for Thyroid Cancer

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Keywords
Thyroid carcinoma · Lenvatinib · Bioelectrical impedance analysis · Weight loss

Abstract
Weight loss is one of the most frequent adverse events during treatment with multikinase inhibitors, but scanty data are available on its extent and characteristics. This is the first assessment of the body composition by bioelectrical impedance analysis and of circulating leptin and ghrelin levels, in patients with advanced thyroid cancer before and at regular intervals during treatment with the tyrosine kinase inhibitor lenvatinib. Body mass index (BMI) decreased in all patients, with an average Δ reduction of –6.4, –9.8, and –15.3% at 3, 6, and 12 months of treatment, respectively. Interestingly, in most patients, after the first year of treatment, BMI remained stable. In all patients, fat mass (FM) reduced more than fat-free mass, the highest decrement being of –60 and –16%, respectively. A decrease in the body cell mass, a parameter mainly due to muscle tissue, was observed only in patients with a vast baseline muscular mass. Total body water decreased in parallel to BMI. During treatment, leptin tightly paralleled the decrease of BMI values, consistent with the decrease in FM, whereas ghrelin levels increased upon BMI decrease. The loss of the FM accounts for the largest portion of BMI reduction during lenvatinib treatment. The increase in ghrelin could account for the BMI stabilization observed after 1 year of treatment. Nevertheless, oral nutritional supplements should be given as early as possible and athletic patients should be encouraged to maintain physical activity. In some circumstances, parenteral nutrition is required for the rehabilitation of these patients.

Introduction

In cancer patients, weight loss is a progressive wasting symptom mainly characterized by loss of adipose tissue and skeletal muscle. It is defined as a medical problem when at least 10% of a person's body weight has been lost in 6 months or 5% in the previous month [1]. The etiology of cancer-related cachexia, a metabolic syndrome driven by inflammation and characterized by loss of muscle independently of the fat mass (FM), is multifactorial, including

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Table 1. BMI (kg/m^2) of the 11 patients in relation to age, gender, and lenvatinib dose

Number of patients	Gender	Age at TKI start, years	Lenvatinib dose, mg	BMI pre-lenvatinib	3rd month assessment	Δ, %	6th month assessment	Δ, %	12th month assessment	Δ, %	Last assessment (months of FU)	Δ, %
1	Female	76	10	24	21.4	−10.8	22.4	−6.7	21	−12.5	20.7 (33)	−13.8
2	Female	60	14	34.7	34	−2.1	32.2	−7.2	30.8	−11.2	30.6 (33)	−11.8
3	Female	74	10	49.6	48.9	−1.4	47.6	−4	40.4	−18.5	28 (27)	−43.5
4	Male	69	24	32.8	30.6	−6.7	30	−8.5	26.2	−20.1	26.7 (21)	−18.6
5	Male	60	24	26.2	25	−4.6	24.1	−8	22	−16	20.4 (21)	−22.1
6	Female	76	10	21.1	18.8	−10.9	19.2	−9	19.4	−8.1	18.8 (21)	−10.9
7	Male	67	20	30.8	26.1	−15.3	23.2	−24.7	24.5	−20.5	24.5 (12)	−20.5
8	Female	45	24	32.9	29.9	−9.1	27.9	−15.2	–	–	27.9 (6)	−15.2
9	Female	84	4	19.2	18.7	−2.6	18.4	−4.2	–	–	18.4 (6)	−4.2
10	Male	21	24	25.9	25.7	−0.8	23.2	−10.4	–	–	23.2 (6)	−10.4
11	Male	66	24	35.8	33.5	−6.4	32.4	−9.5	–	–	32.4 (6)	−9.5
Average BMI Δ variation						−6.4		−9.8		−15.3		

BMI Δ variations during FU, with respect to baseline values, are reported. BMI, body mass index; TKI, tyrosine-kinase inhibitor; FU, follow-up.

complications caused by the malignancy, treatment, or physical and mental status [2]. Scanty data are available in patients with thyroid cancer (TC). In particular, 3 studies on limited number of patients with differentiated TC reported no changes in body weight or body composition during the follow-up (FU) [3]. No data are available on advanced TC patients, though in the real life practice no weight loss is usually recorded even when a high metastatic tumor burden is present, likely due to the biological characteristics of this tumor, which has a relatively low growth rate and is poorly symptomatic. Nevertheless, patients experience a relevant weight decrease when treatment with a tyrosine kinase inhibitor (TKI) is started, such as lenvatinib, which is a potent inhibitor of vascular endothelial growth factor receptors, currently used for advanced, radioiodine refractory differentiated TC [4]. In the registration study, as in the "real life" following reports, weight loss occurred in 46–92% of cases [4–9]. Weight loss may reach worrisome levels, with loss of up to the 25% of the baseline weight, and a transient or definitive dose reduction or drug interruption is required, always associated with a reduction of the therapeutic effect of the compound. To date, no data are available on the characteristics of the weight loss during TKIs in patients with advanced TC, though a better knowledge of such phenomenon could give insights into its more appropriate management. To better define the weight loss observed in TC patients on lenvatinib, we performed at regular intervals during treatment, a bioelectrical impedance analysis (BIA), which is a reliable method to evaluate body composition, used in several diseases, including cancer [10, 11]. BIA prediction equations have been cross validated with MRI for the evaluation of whole-body skeletal mass [12] and of fat-free mass (FFM) [13] and with CT for the estimation of visceral fat [14].

Body weight and energy balance are regulated by 2 hormones, leptin and ghrelin [15]. Leptin is released into the circulation by the adipose tissue as a function of the energy stores. Consistently, leptin levels are correlated with body mass index (BMI), being higher in subjects with a higher BMI and a higher percent of body FM [16]. Similarly, the secretion of ghrelin by the stomach largely depends on the nutritional state. Ghrelin levels are negatively correlated with BMI in humans, increasing when obese lose weight, and decreasing when anorexic patients gain weight, suggesting that ghrelin changes in response to dieting to maintain body weight [17]. Hence, we measured leptin and ghrelin levels at baseline and during treatment with lenvatinib.

Materials and Methods

We enrolled 11 consecutive patients with advanced radioiodine refractory differentiated TC during treatment with lenvatinib, followed-up at a single Institution. The clinicopathological features of the patients as well as the response to treatment and the adverse events recorded are reported in online supplementary Table 1 (see www.karger.com/doi/10.1159/000504048 for all online suppl. material). All patients underwent anthropometric measurements including age, sex, weight, height, and BMI (kg/m^2) before starting TKI treatment and at each FU visit. In addition, we performed in all patients the body composition assessment by Biolectrical Body

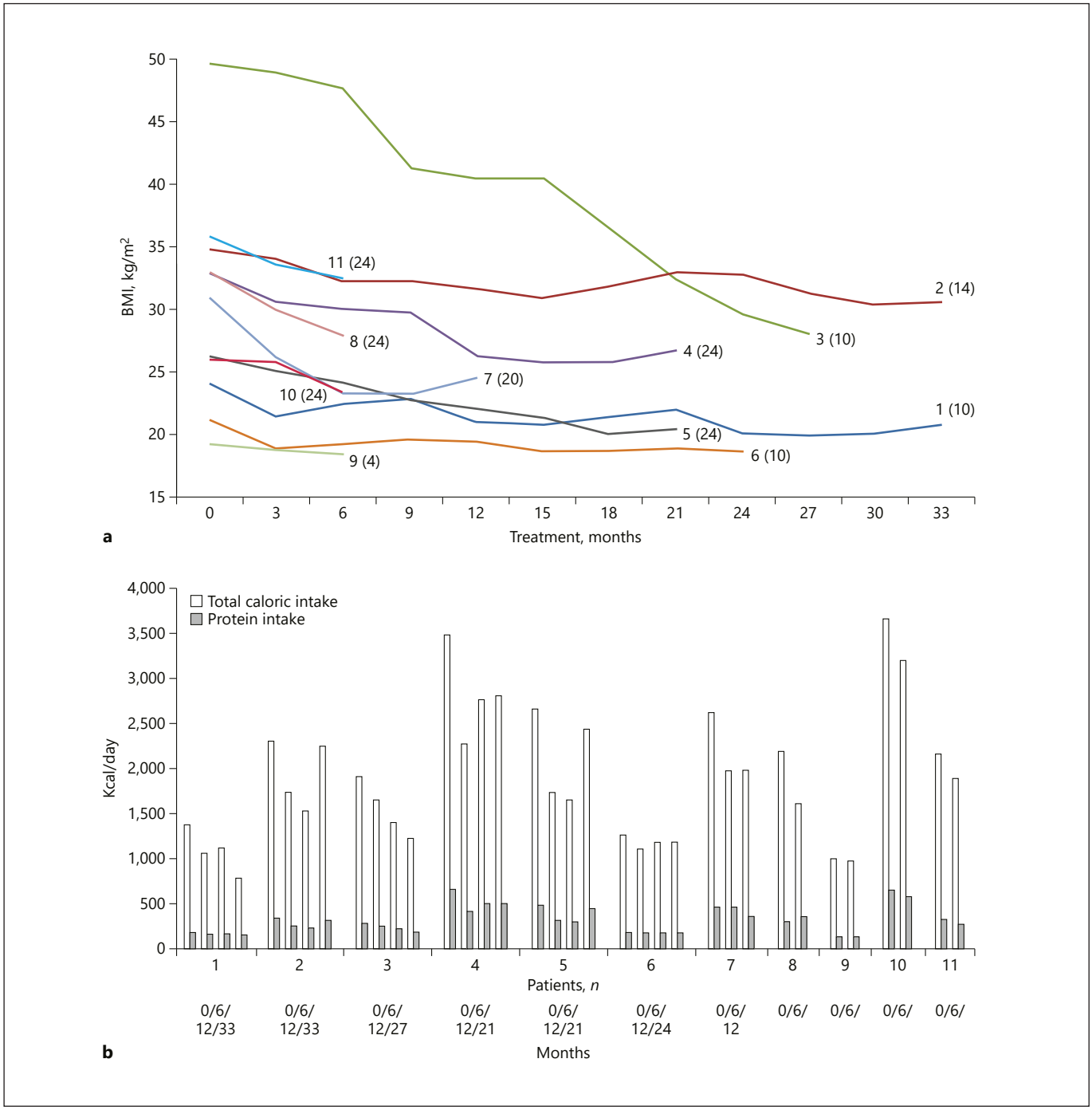


Fig. 1. a BMI trend at baseline and during treatment with lenvatinib in patients with advanced radioiodine refractory TC. The dosage of the drug is reported into square brackets. BMI, body mass index. **b** Calorie and protein intake of the patients. According to the length of FU, we reported data at 0 and 6 months, or at 0, 6, and 12 months, or at 0, 6, 12, and last FU visit (indicated in the Table below the graph). Physical activity: patients 5, 7, and 10 had an agonist activity, which has been progressively reduced and then stopped in 2 of them, whereas it has be continued at the same level for patient 10. The remaining 8 patients had a sedentary life style before the start of the TKI treatment, their physical activity being limited to the caring of familial activities (such as houseworks, shopping). These patients experienced a progressive reduction of these activities during treatment, mostly related to fatigue, though never interrupting them. BMI, body mass index.

Composition Analyzer (BIA) using proprietary equations AKERN (BIA 101 Anniversary with analysis software BodygramPlus 1.1.0.10, Akern 2014, Florence, Italy – Janssen), which have been cross compared and validated with public domain equations, and currently used in several clinical and epidemiological studies [18, 19]. BIA measures whole-body impedance, the opposition of the body to alternating current consisting of 2 components: resistance (R) and reactance (Xc). Using the values of resistance and reactance and the parameters of age, sex, weight, and height of each subject, predictive equations of the various body compartments are obtained. We analyzed 5 composition parameters in all patients: FM (kg), FFM (kg), body cell mass (BCM, kg), and total body water (TBW, L). The contribution of these parameters to the body weight is reported in online supplementary Figure 1. Moreover, we evaluated the phase angle (PhA), which is a marker of the fluid distribution between the intra and extracellular medium and reflects nutritional and functional status of the subjects [20, 21].

Although it may not be as accurate for estimation of body composition as other methods, such as DXA, we used BIA because it is a widely used, portable method, which can be repeated frequently. Moreover, it is easy and quick to perform, at the time of the routine control visits, thus limiting the stay in the Hospital for these compromised patients [22, 23]. Patients were evaluated at 3-month intervals and the longest FU was of 33 months. All patients followed their normal dietary regimen, integrated by oral hypercaloric supplements (200–250 kcal/100 mL) in patients 1, 7, 8. Patient 5, due to the huge weight loss and anorexia developed after 18 months of treatment, underwent a 3-week recovery and received 24-h parenteral nutrition (955 kcal/L/day). It is worth to note that the starting dose of lenvatinib was not modified during the FU in any patient. The calorie and protein consumption was calculated for each patient at the basal evaluation and every 6 months during the FU.

In 9/11 patients, leptin (Leptin Sandwich ELISA- DRG International Inc., Springfield, NJ07081, IL, USA) and total ghrelin (Human Ghrelin Coated ELISA-Thermofisher, Waltham, MA, USA) were measured at baseline and during the FU. As biochemical parameters of nutritional status, hemoglobin (n.v. 11.9–16 g/dL), lymphocytes (n.v. 0.9–5.4 $\times$ 10^9/L), and albumin (3.2–5.2 g/dL) were evaluated in all patients at each FU visit.

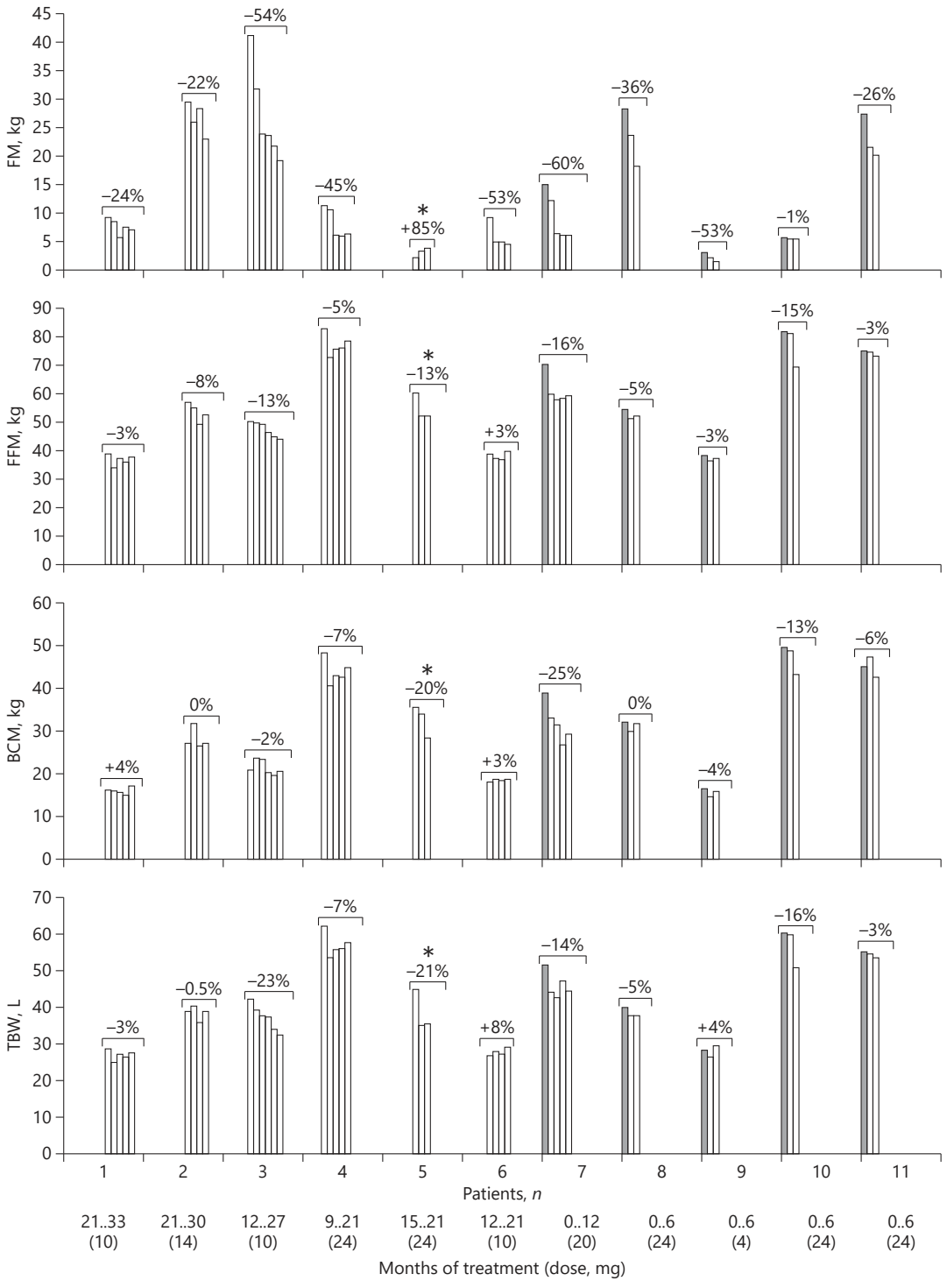
As a control group, we evaluated the possible weight modifications during the FU in 20 patients with advanced, persistent, and metastatic TC, never treated with TKIs.

All patients gave written informed consent for the treatment for scientific purposes of their clinical data. The study did not require the approval of an independent Ethical Committee since patients were submitted to protocols approved by the Institutional Review Board (Ethical Committee of the Istituto Auxologico Italiano IRCCS, Milan-Italy) and routinely applied in the clinical practice.

Results

During lenvatinib treatment, a BMI decrease was observed in all cases, with a delta reduction at last FU assessment ranging 4–43% (Table 1). All patients experienced the weight loss as earlier as the 3rd–6th month after the start of lenvatinib (Fig. 1a). The mean BMI delta reduction was of 6.4% at 3 months (range 0.8–15.3%), of 9.7% at 6 months (range 4–24.7%), and of 15.2% at 12 months (range 8.1–20.5%). Among the 6/11 patients with a duration of treatment longer than 1 year, a stabilization of the BMI was observed in 5, while in patient 3, weight continued to decrease (Table 1, Fig. 1a). Parallel data came from the sequential evaluation of the basal caloric intake (Fig. 1b). Interestingly, no significant weight variations during the FU were observed in the 20 control patients with advanced metastatic TC, never treated with TKIs (online suppl. Table 2). The bioimpedentiometric data (FM, FFM, BCM, and TBW) are shown for all patients in Figure 2 and in online supplementary Table 3. In the 5 patients (7–11) with available basal data, FM and FFM reduced in the following 3–12 months of FU, by a delta reduction ranging 1–60% and 3–16% for FM and FFM, respectively. In the remaining 6 patients (1–6), BIA evaluations were started during the FU. In those cases, a decrease in the FM parameter was observed in 5 patients (decrement range 22–54%), while an increase was found in patient 5 as a consequence of the parenteral treatment performed during a 3-week recovery. As regards FFM, a delta reduction of 3–13% was observed in 5/6 cases, while patient 6 experienced a slight FFM increase, likely related to the resumption of physical activity after a long period of recovery for pneumonia. Three patients (1, 6, and 9) had a stable FFM. These patients had the lowest FFM baseline levels, were the oldest ones (age ranged between 76 and 84 years old), and were treated with the lowest doses of lenvatinib (4 and 10 mg). No correlation was found between loss of FFM and the ECOG status, and/or the degree of fatigue reported by patients (online suppl. Table 4). Interestingly, regardless of the differences among patients, the decrease in FM was invariably higher

Fig. 2. FM, FFM, BCM, and TBW levels evaluated by bioimpedentiometric analysis during treatment with lenvatinib (the dosage of the drug is reported into square brackets). Dark columns indicate baseline levels that were available for patients 7–11. The delta decrements/increments between the first and the last available assessments are reported, too. The asterisk indicates that patient 5 underwent a 3-week parental nutrition during the 18th month of treatment. Measurements were taken after 5 min of rest by placing a pair of electrodes between the wrist and the right ankle with the subject in the supine position, with legs slightly apart, and the arms not touching the body. Patients removed earrings, rings, watches, and metal objects; they were fasting and had not undergone intense exercise before the measurement. Finally, BIA measurements were always done by the same operator. TBW, total body water; BCM, body cell mass; FFM, fat-free mass; FM, fat mass. *(For figure see next page.)*


FM, kg
FFM, kg
BCM, kg
TBW, L
–24%
–22%
–54%
–45%
*
+85%
–53%
–60%
–36%
–53%
–1%
–26%
–3%
–8%
–13%
–5%
*
–13%
+3%
–16%
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+4%
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–20%
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1
2
3
4
5
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11
Patients, n
21..33 (10)
21..30 (14)
12..27 (10)
9..21 (24)
15..21 (24)
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Months of treatment (dose, mg)

2

than that of FFM, in patients evaluated either from baseline or only during treatment, with the only exception of patient 10. This 21 years-old man had a low FM level at baseline which remained stable during treatment, but a reduction in FFM (–15%) was observed (Fig. 2). BCM modification was variable among our patients, ranging from slight or null (–7 to +4%) in 8 cases to 13–25% reduction in cases 5, 7, and 10. Interestingly, in patient 5, this trend continued despite the parenteral nutrition. TBW decreased in parallel to weight loss. The higher was the BMI lost, the higher was the TBW reduction. In particular, patients whose TBW reduced the most (14–23%), had lost >20% of the baseline BMI (Fig. 2). Finally, none of our patients showed any variation in the PhA (online suppl. Fig. 2).

Interesting and original findings derive from the serial evaluation of the leptin and total ghrelin levels in all included patients. Basal leptin levels ranged 1.11–40.84 in females (n.v. 3.6–11.1 ng/mL) and 1.15–4.69 in males (n.v. 2–5.6 ng/mL), whereas basal total ghrelin ranged 153.3≥1,000 in females and 256.36–993 in males (n.v. normal weight: 550–650 pg/mL, obese: 200–350 pg/mL, underweight: >1,000), according to BMI values which were 18.5–49.5 in females and 22.6–35.8 in males (normal weight 18.5–24.9). In particular, the lowest leptin levels and the highest ghrelin levels were observed in normal or underweighted patients. During FU determinations, in all patients, leptin tightly paralleled the oscillations of BMI values, consistent with the decrease/increase in FM, whereas ghrelin had an opposite trend, its increase corresponding to the decrease in body weight (Fig. 3, 4).

Finally, the biochemical parameters of nutritional status (hemoglobin, lymphocytes, and albumin), which are usually altered during neoplastic cachexia, did not show relevant changes during the FU in any of our patients (data not shown).

Discussion

We report for the first time the evaluation of the impact of lenvatinib treatment on anthropometric parameters and body composition in patients treated for advanced RAI-R TC. Weight loss is one of the most frequent adverse events of lenvatinib treatment (50–90% of patients) [24]. In our series, BMI decreased in all patients, with an average delta reduction with respect to baseline of –6.4, –9.7, and –15.2% at 3, 6, and 12 months of treatment, respectively. Interestingly, in most patients, after the first year of treatment, BMI remained almost stable. The bioimpedentiometric analyses showed that FM and FFM were affected, though the highest reduction was related to the loss of FM, which is likely the first compartment involved, in particular in overweight and obese patients. Some data on this topic have been obtained with other TKIs. By computed tomography analysis in patients with renal carcinoma, sorafenib was found to exacerbate muscle loss after 6 months of therapy [25], and axitinib treatment resulted in a decrease in skeletal mass and subcutaneous adipose tissue [26]. Based on these reports, weight loss has been usually related to a prevalent decrease in FFM possibly due to the inhibition by TKIs of pathways involving MAPK/ERK kinases, which are involved in the induction of muscle anabolism [27]. Moreover, the fatigue frequently reported by patients during TKI treatment [28] contributes to the reduction of the physical activity, likely leading to FFM loss. In our series, neither the fatigue nor the ECOG status correlate with FFM decrease, which was indeed recorded only in the 3 male patients (5, 7, and 10), who had an intense competitive level physical activity (cycling, walking, basket, respectively) before starting treatment. Consistent with these data is the lack of significant variation of BCM, a parameter based on muscle tissue (60%), organ tissue (20%), and red cells/tissue cells (20%). This latter finding, together with the normal levels of the biochemical parameters of nutritional status, and with the lack of modification in the PhA, which reflects the nutritional and functional status, indicates that our patients are not undernourished and are not experiencing a neoplastic cachexia. Consistently, we did not find any weight variation in a control group of 20 patients with advanced and metastatic TC, never treated with TKIs. In our patients on lenvatinib the weight loss was mostly due to the significant reduction of FM, which could be due to at least 2 reasons. First, as demonstrated in the present series, the reduced nutritional intake related to anorexia and to stomatitis and dysgeusia reported in 20–70% of cases in the registrative and "real life" studies [24]. Moreover, diarrhea is frequently present (45–70% of cases) [24] and contributes to the reduction in the absorption of nutrients and to the liquids loss, as highlighted by the decrease in TBW found in all patients, paralleling the BMI. Second, since adipose tissue is highly vascularized, and its expansion involves the development of the tissue vascular network [29], results in animal models predicted antiangiogenic cancer therapies to inhibit adipose tissue mass and to increase risk of significant weight loss in treated patients [30].

In order to obtain further insights on the regulation of food intake and body weight in these patients, the ghrelin

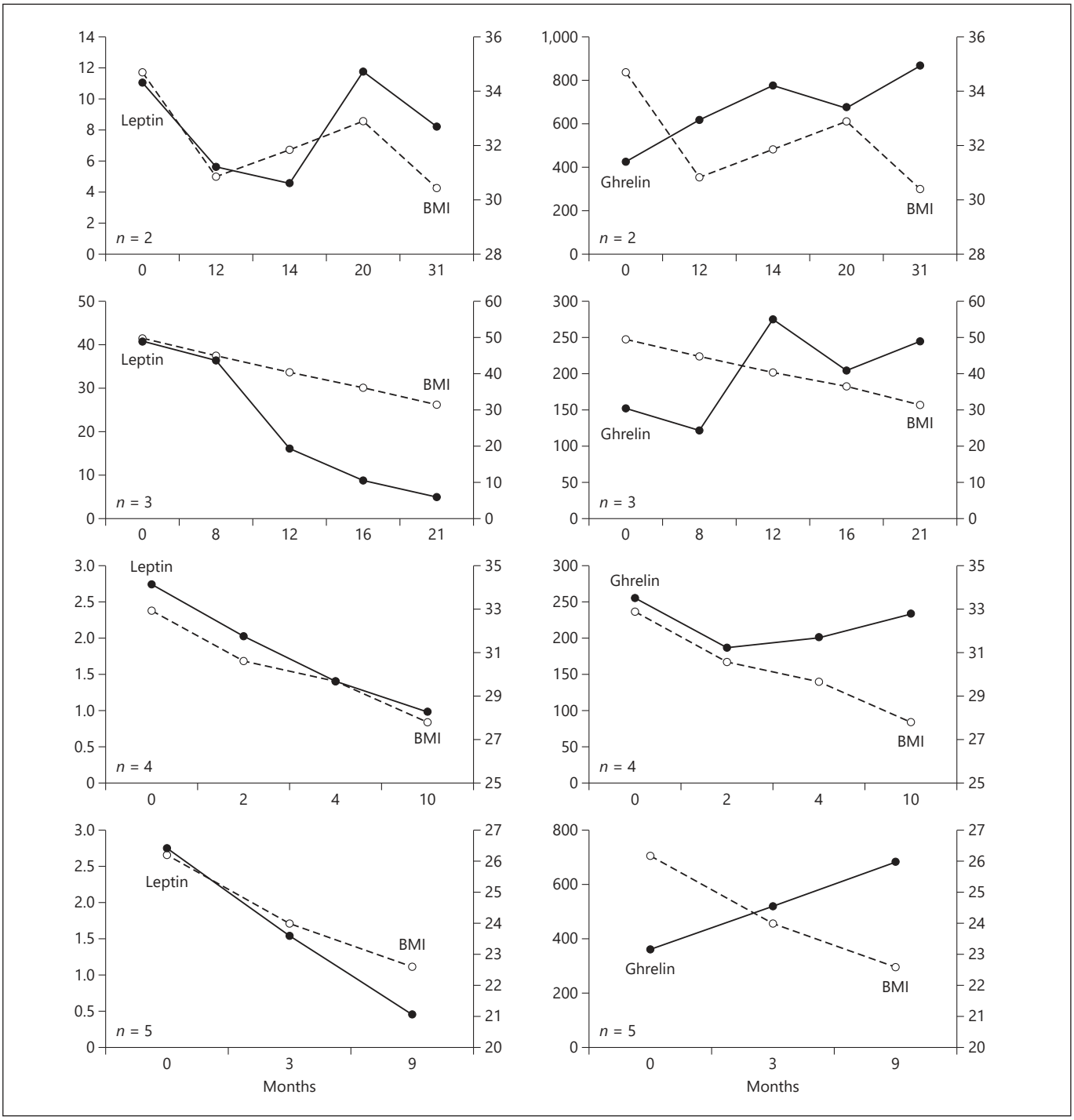

Fig. 3. Leptin, ghrelin, and BMI pattern at baseline and during treatment with lenvatinib in patients 2–5. Leptin and ghrelin levels are reported on the left axes with a unit of measure of ng/mL and pg/mL, respectively. BMI values are reported on the right axes (kg/m^2). Leptin (Leptin Sandwich ELISA- DRG International Inc., Springfield, NJ07081 IL, USA) and total ghrelin (Human Ghrelin Coated ELISA-Thermofisher, Waltham, MA, USA). Samples were taken always between 8 and 8.30 a.m., fasting. Normal values for leptin are 3.6–11.1 ng/mL (females) and 2–5.6 ng/mL (males), whereas normal values for total ghrelin are 550–650 pg/mL (normal weight), 200–350 pg/mL (obese), and >1,000 (underweight). BMI, body mass index.

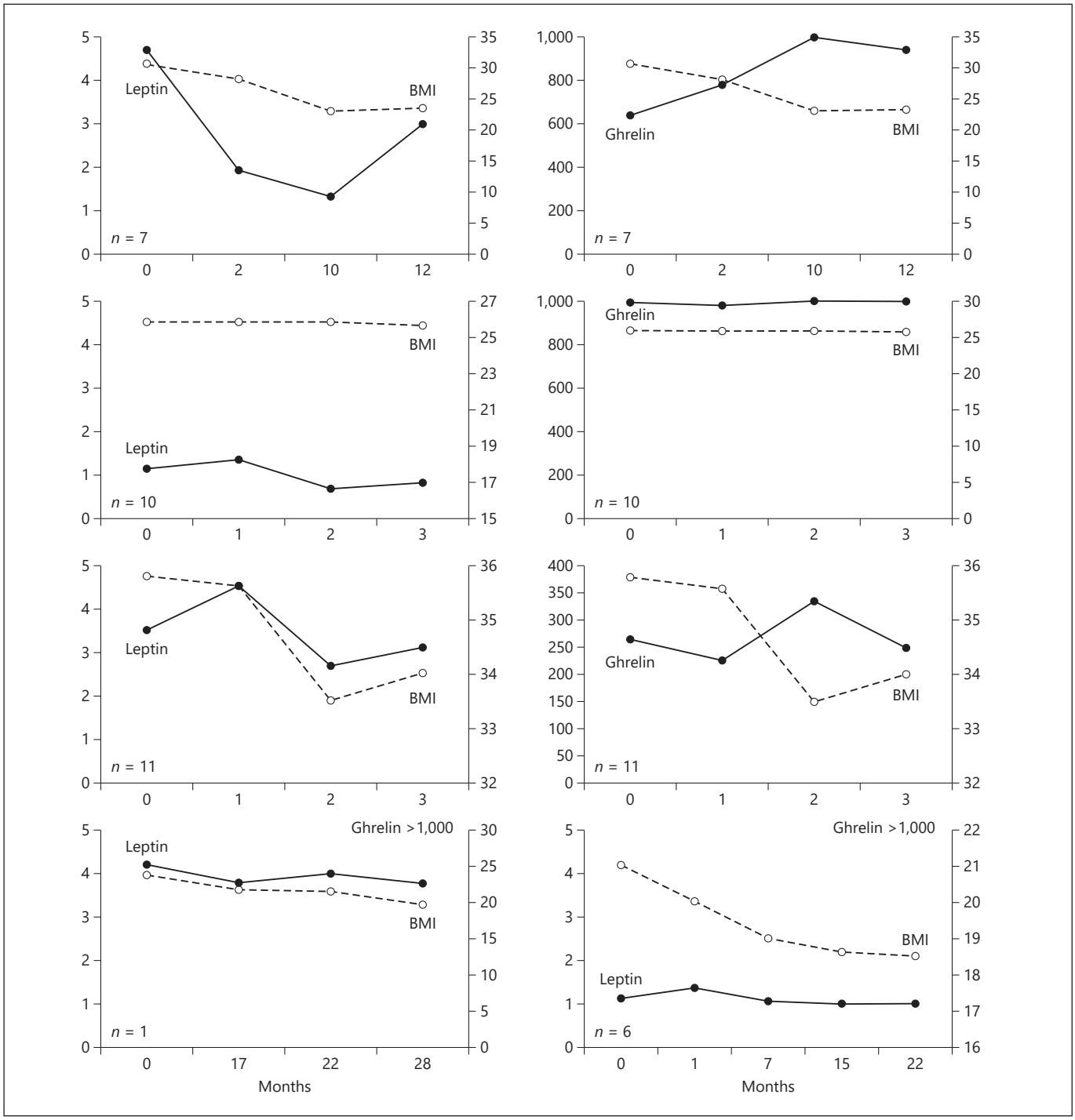

Fig. 4. Leptin, ghrelin, and BMI pattern at baseline and during treatment with lenvatinib in patients 7, 10, and 11. For patients 1 and 6, we reported on the graph only leptin levels, since ghrelin was stably >1,000 pg/mL, consistent with the low BMI of these 2 patients. Leptin and ghrelin levels are reported on the left axes with a unit of measure of ng/mL and pg/mL, respectively. BMI values are reported on the right axes (kg/m^2). BMI, body mass index.

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and leptin levels were measured at baseline and during FU. Both leptin and ghrelin showed a behavior similar to that observed in anorexia nervosa or underweight [31]. They had a strong correspondence with BMI values, leptin tightly paralleling the decrease in the BMI, consistent with the reduction of the FM, the main site of leptin synthesis. On the other hand, ghrelin had an opposite trend, increasing in response to starving to stimulate food intake and to counteract body weight loss. This phenomenon could contribute to the BMI stabilization observed in the majority of our patients after 1 year of treatment.

A potential drawback of this study is the lack of BIA baseline determinations for all patients. Nevertheless, since the evaluations were performed in different periods of treatment, the whole of the data gives the longitudinal design of the nutritional status after the start of lenvatinib. On the other hand, this is the first study giving insights, including BIA and leptin/ghrelin evaluations, into the weight loss observed during lenvatinib treatment in a series of patients with a long FU and uniformly treated by the specialists of a single tertiary center. Hence, we consider our data extremely relevant for clinicians, though they certainly need to be confirmed in controlled trials, which could also investigate the effect of dose reductions and/or other interventions both pretreatment and during treatment.

A close monitoring and management of weight loss is crucial to avoid withdrawal and to limit the need for dose reduction, which may affect the treatment response. Our data indicate that the possibility to reduce weight loss by exercise training, as suggested for cancer-related cachexia [32], seems to be of limited value in nonathletic patients treated with lenvatinib since most of the weight loss is related to the FM. On the other hand, expert nutritionist interventions are needed and often slow down the weight loss rate, especially if they are started immediately after the beginning of lenvatinib. In patients used to an agonistic or semi-agonistic sport level, a decrease in FFM is also observed and should be counteracted encouraging feeding supplementation and the maintenance of physical activity during treatment.

Statement of Ethics

All study participants provided a written informed consent.

Disclosure Statement

S.D.L., C.C., M.D.S., A.D., and L.P. have no conflicts of interest to declare. L.F. has a consultant relationship with Eisai.

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Author Contributions

S.D.L.: design of the study, data collection and analyses, writing of manuscript draft. C.C., M.D.S., and S.C.: data collection and analyses. A.D.: biochemical analyses and data interpretation. L.P.: data interpretation and revision of the final paper. L.F.: design of the study, data interpretation, and writing of the final manuscript.

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