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A case of squamous cell lung cancer treated with anamorelin in combination with a multidisciplinary collaborative approach for treating cancer cachexia

Yuri Oshima [a,*], Hiroyuki Matsuura [a], Yusuke Sakurai [a], Kaho Hirai [a], Eriko Tani [a], Naoki Yoshimoto [a], Kenichi Minami [a], Fumio Yamasaki [b], Mayu Nishime [c], Tomonori Hirashima [d]

[a] Department of Respiratory Medicine, Ishikiriseiki Hospital, Osaka, Japan
[b] Division of Rehabilitation, Ishikiriseiki Hospital, Osaka, Japan
[c] Division of Nutrition Management, Ishikiriseiki Hospital, Osaka, Japan
[d] Department of Thoracic Oncology, Ishikiriseiki Hospital, Osaka, Japan

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ABSTRACT

Anamorelin (ANA) is approved for treating cancer cachexia (CCX) in Japan. We report the case of a 69-year-old man with stage IVB squamous cell lung cancer complicated by CCX, having a 13.6% weight loss in 6 months. After chemotherapy was initiated, his weight was further reduced. Therefore, we started ANA combined with a treatment approach by a multidisciplinary collaboration, including nutritionists and physical therapists. After initiation of ANA, the body weight, appetite, psoas muscle index, and physical functions rapidly improved during chemotherapy. ANA administration combined with a multidisciplinary collaboration approach can be an effective supportive therapy against CCX during chemotherapy.

1. Introduction

Cancer cachexia (CCX) is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without the loss of fat mass) that cannot be fully reversed by conventional nutritional support and which leads to progressive functional impairment [1]. Specifically, the following changes may occur: body weight loss (BWL) of ≥5% within 6 months, BWL of ≥2% in patients with a body mass index (BMI) of <20 kg/m^2, or BWL of ≥2% in patients with sarcopenia [1]. CCX is classified into the following three stages: pre-CCX, CCX, and refractory CCX. Furthermore, CCX is associated with worse survival in patients with non-small cell lung cancer (NSCLC) [2].

Currently, anamorelin (ANA) (100 mg/day orally) is an approved drug in Japan for improving body weight (BW), lean body mass (LBM), and appetite in CCX patients with NSCLC, gastric cancer, colon cancer, and pancreatic cancer, excluding cases of pre-CCX and refractory CCX [3–5]. ANA is an orally active, high affinity, selective ghrelin-like agonist of the ghrelin receptor. Ghrelin, a peptide hormone secreted from the stomach, was discovered by Kojima and Kangawa in 1999 [6]. In humans, ghrelin significantly increases

Abbreviations: ANA, anamorelin; BMI, body mass index; BW, body weight; BWL, body weight loss; CCX, cancer cachexia; CT, computed tomography; LBM, lean body mass; NSCLC, non-small cell lung cancer; PMI, psoas muscle index.

* Corresponding author. Department of Respiratory Medicine, Ishikiriseiki Hospital, 18-28, Yayoi-chou, Higashi-Osaka city, Osaka, 579-8026, Japan.
E-mail address: y-ooshima@ishikiriseiki.or.jp (Y. Oshima).

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food intake and appetite by increasing growth hormone (GH) [7]. A previous study [8] indicated that, similar to ghrelin, ANA is a potent and highly specific ghrelin receptor agonist with significant appetite-enhancing activity, leading to increases in food intake and BW and a stimulatory effect on GH secretion.

The European Society for Medical Oncology Clinical Practice Guidelines recommend a multidisciplinary collaboration approach for treating CCX that includes nutrition, muscle training, and social support in addition to drug therapy [9]. Based on this recommendation, we treated CCX in a patient with squamous cell NSCLC undergoing chemotherapy (the day of initiation was set as day 1) through a multidisciplinary collaboration among a physician, physical therapists, and nutritionists, in addition to providing ANA therapy, as reported here.

2. Case report

On day −18, a 69-year-old man who was a current smoker (49 pack-years) visited a primary care clinic with a chief complaint of BWL with general fatigue and appetite loss. A chest X-ray revealed a large nodular shadow in the right upper lobe (Fig. 1), and low hemoglobin and high C-reactive protein levels were observed following blood tests. Therefore, the patient was referred to our hospital on day −13. The patient underwent fiberoptic bronchoscopy on day −12 as well as staging through computed tomography (CT), magnetic resonance imaging, and positron emission tomography. Consequently, the patient was diagnosed with squamous cell NSCLC with interstitial pneumonitis and was staged as cT4N0M1c (stage IVB with multiple liver metastases), as shown in Fig. 1. Subsequently, the patient was admitted to our hospital on day 0. His height, BW, and BMI were 168.0 cm, 51.7 kg, and 18.3 kg/m^2, respectively. Thus, he was diagnosed with CCX having a BWL of 13.6% in 6 months. His vital signs on admission were as follows: consciousness, clear; body temperature, 36.8 °C; blood pressure, 93/65 mmHg; oxygen saturation at rest, 97%. The physical examination revealed the following: performance status, 1; cardiac sounds, no murmur; chest auscultation, fine crackles in both lungs; body surface findings, not particular. Laboratory findings were as follows: white blood cell count, 8940 cells/μL; red blood cell count, 379 × 10^4 cells/μL; hemoglobin level, 11.1 g/dL (10 months ago: 16.0 g/dL); platelet count, 49.1 × 10^4 platelets/μL; C-reactive protein, 11.49 mg/dL; albumin, 2.6 g/dL; blood sugar, 108 mg/dL.

Chemotherapy with carboplatin (area under the concentration-time curve, 6 mg/mL/min) was initiated on day 1 of a 21-day cycle, and nanoparticle albumin-bound paclitaxel (100 mg/m^2) was administered on days 1, 8, and 15 of a 21-day cycle. Unfortunately, despite a diet remedy prescribed by nutritionists, his appetite decreased to grade 2 based on the Common Terminology Criteria for Adverse Events, and accordingly, his BW further decreased to 49.0 kg on day 15. Therefore, we decided to initiate oral ANA administration 100 mg/day every day at his wake-up time.

Before ANA initiation, on day 15, physical therapists performed the following function tests: measurement of lower leg circumference (cm), strength, assistant walking, rising from a chair, climbing stairs, and falls (SARC-F) score; short physical performance battery; handgrip strength (kg), measured by a GT-1201-D dynamometer (OG Wellness Co., Ltd., Okayama, Japan); gait speed (m/s) to walk 4 m, measured twice using a TD-392 stopwatch (Tanita Co., Ltd., Tokyo, Japan); sit-to-stand test (s), measured by a TD-392 stopwatch (Tanita Co., Ltd., Tokyo, Japan) and requiring five repetitions of moving from a 40-cm chair to standing position. Simultaneously, a physical therapist instructed the patient to self-exercise 10 times each on the left and right separately, 1 to 3 sets a day, as follows: thigh rising while sitting; heel rising while holding a handrail; performing a squat exercise while holding a handrail; getting up from a chair.

After ANA was started on day 16, his appetite rapidly improved from Common Terminology Criteria for Adverse Events grade 2 to

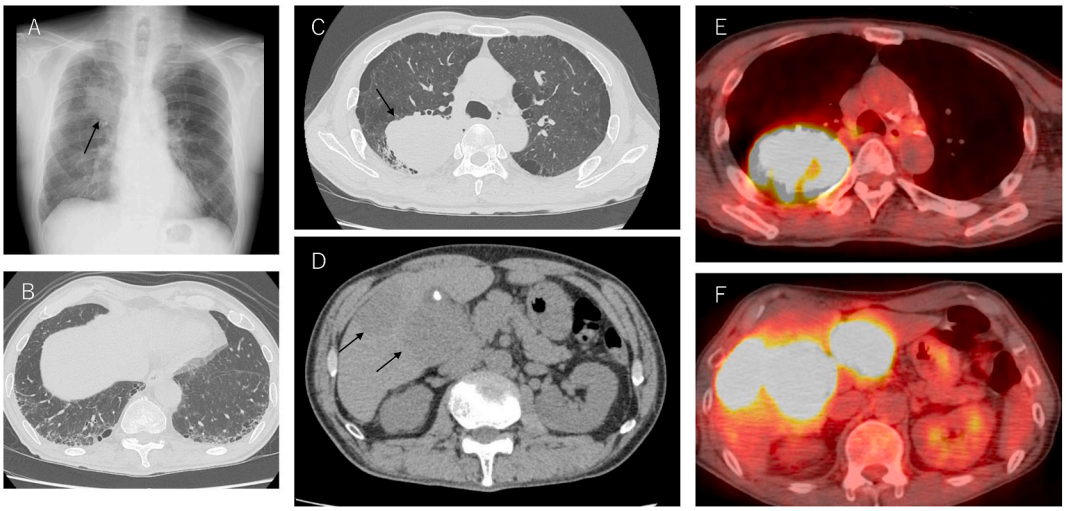

Fig. 1. Radiological image findings. A: Chest X-ray on day −16 revealing a large nodule shadow in the right upper lobe (RUL) (arrowhead). B, C, and D: Computed tomography on day −13 showing interstitial pneumonitis, a 73 × 55 × 65 mm tumor in the RUL (arrowhead), and tumors in the liver (arrowhead). E, F: Positron emission tomography on day −7 showing a high fluorodeoxyglucose uptake in the lung tumor and the liver.

0 within 7 days. The patient was discharged on day 17 and started self-exercise, which was performed mildly at first and then gradually more strictly. Table 1 shows the changes in his BW, BMI, functional assessment of anorexia/cachexia treatment score, and nutrition indicators. The patient continued to receive chemotherapy without interruption until he developed grade 3 bacterial pneumonia. Although pneumonia improved, chemotherapy was completed in 5 cycles. As shown in Fig. 2, the primary lesion and liver metastases shrank without deterioration of interstitial pneumonitis. Furthermore, almost all physical measures and function test results improved after ANA was initiated (Table 2). Fig. 3 shows the psoas muscle index (PMI, cm^2/m^2) measured at the caudal end of the L3 level by image-processing software (Image J: National Institutes of Health, Bethesda, MD, USA), as previously described [10]. The PMI increased from 4.42 cm^2/m^2 before ANA initiation on day −7 to 5.12 cm^2/m^2 after the initiation on day 92; however, this was still lower than the Asian male cutoff of 6.36 cm^2/m^2 [11]. Furthermore, as shown in Fig. 3, both subcutaneous and visceral fat on CT increased, similar to the PMI changes.

Nutrition counseling was performed four times by nutritionists before and after ANA was initiated. Before ANA was initiated, they suggested an easy-to-eat diet to the patient and his family to increase his appetite. However, after receiving ANA, the patient ate sweet buns after each meal in addition to the three meals in the morning, noon, and evening. Such excessive food intake led to an increase in blood sugar levels, as shown in Table 1. Therefore, on day 57, the nutritionists and the physician advised the patient and his family that he follow a well-balanced diet, avoiding excessive food intake. The patient and his family followed the recommendations with continued strict self-exercise.

3. Discussion

This case showed a rapid improvement in appetite loss and BWL, associated with worsening CCX, within 7 days after initiation of ANA therapy while undergoing chemotherapy. This rapid improvement suggests the efficacy of ANA, rather than the effectiveness of the chemotherapy. In this patient, the unusual excessive food intake began immediately after ANA administration while mild self-exercise was being performed. Therefore, the improvement could not be attributed to the self-exercise but the strong appetite-enhancing effect of ANA.

Furthermore, the multidisciplinary collaboration of nutritionists and physical therapists, in addition to the drug therapy, improved the patient's eating habits, PMI, and physical functions. Nutrition counseling by nutritionists did not suggest an easy-to-eat diet but assisted in controlling excessive food intake by the appetite-enhancing effect of ANA. Self-exercise assisted in recovering physical function and increasing fat and PMI in a well-balanced manner.

The prevalence of CCX in lung cancer patients is 25.8% [12]. CCX is caused by systemic inflammation and the increased energy expenditure of cancer cells [13]. Approximately half of the cancer patients exhibit BWL at the time of cancer diagnosis, and >80% experience it 1–2 weeks before death [14,15]. BWL not only affects the prognosis by shortening the patient's overall survival but also affects the treatment by decreasing the response rate, increasing the treatment failure rate in 3 cycles, and increasing the number of adverse events [13,16]. Thus, CCX control is crucial for cancer treatment.

Corticosteroids [17], nonsteroidal anti-inflammatory drugs [18], and progesterone [19] have been used against CCX; however, their efficacy is limited. ANA, a ghrelin receptor agonist, is an oral drug specific for CCX [20]. Ghrelin, a peptide hormone secreted from the stomach, was discovered by Kojima and Kangawa in 1999 [6]. In Japan, ANA was approved because of its propensity for improving BW, LBM, and appetite in CCX patients with NSCLC [3,4] and patients with gastrointestinal cancer, including gastric, colon, and pancreatic cancer [5]. In studies involving ANA administration in various cancers [3,4], hyperglycemia, diabetes mellitus, first-degree atrioventricular block, and tachycardia were relatively frequent adverse events. However, these adverse events did not appear in our case, even though the patient's dietary habit drastically changed with increased fat on CT after ANA initiation. The absence of such adverse events [3,4] could be attributed to the multidisciplinary collaboration approach used on the patient, which improved physical functions.

In Europe, ANA has not been approved because of its marginal effectiveness in improving LBM and ineffectiveness in improving handgrip strength and quality of life [21]. This finding suggests that ANA alone would not be sufficient as a treatment for CCX. The European Society for Medical Oncology Clinical Practice Guidelines recommend multimodal treatments for CCX [9]. A pilot study [22] comparing a multimodal treatment, consisting of drug therapy, nutritional advice, nutritional treatment, and physical exercise, to standard treatment in 46 patients with solid tumors beginning their chemotherapy revealed that the multimodal treatment improved their BWs. As also shown in a case report of lung cancer [23], a multidisciplinary approach would be required to optimize the survival

Table 1
Changes in BW, BMI, appetite, and nutrition indicators before and after starting anamorelin.

	Weeks after starting anamorelin												
	Before	1	2	3	4	5	6	7	8	9	10	11	12
BW (kg)	49.0	51.9	53.7	54.1	55.1	–	58.9	59.9	58.6	59.1	59.8	59.9	59.7
BMI (kg/m^2)	17.36	18.39	19.03	19.17	19.52		20.89	21.22	20.76	20.93	21.19	21.22	21.15
FAACT score	16	–	–	20	–	–	–	–	–	20	–	–	20
Albumin (g/dL)	2.5	2.5	3.0	3.2	3.3	3.6	3.3	3.3	3.5	3.2	3.3	3.2	2.9
BS (mg/dL)	98	135	112	102	140	108	133	135	109	124	126	113	104
WBC count (/μL)	3160	4000	4320	4870	5080	4740	4150	4420	6000	4510	7030	6390	6010
Hemoglobin (g/dL)	10.2	9.5	10.0	9.7	9.9	9.9	9.8	9.6	10.3	9.8	9.9	9.4	8.8
C-reactive protein (mg/dL)	8.32	0.54	0.82	1.74	0.58	0.19	0.53	0.25	0.73	1.12	2.01	6.07	4.40

BMI, body mass index; BS, blood sugar level after breakfast; BW, body weight; FAACT, Functional Assessment of Anorexia/Cachexia Treatment; WBC, white blood cell.

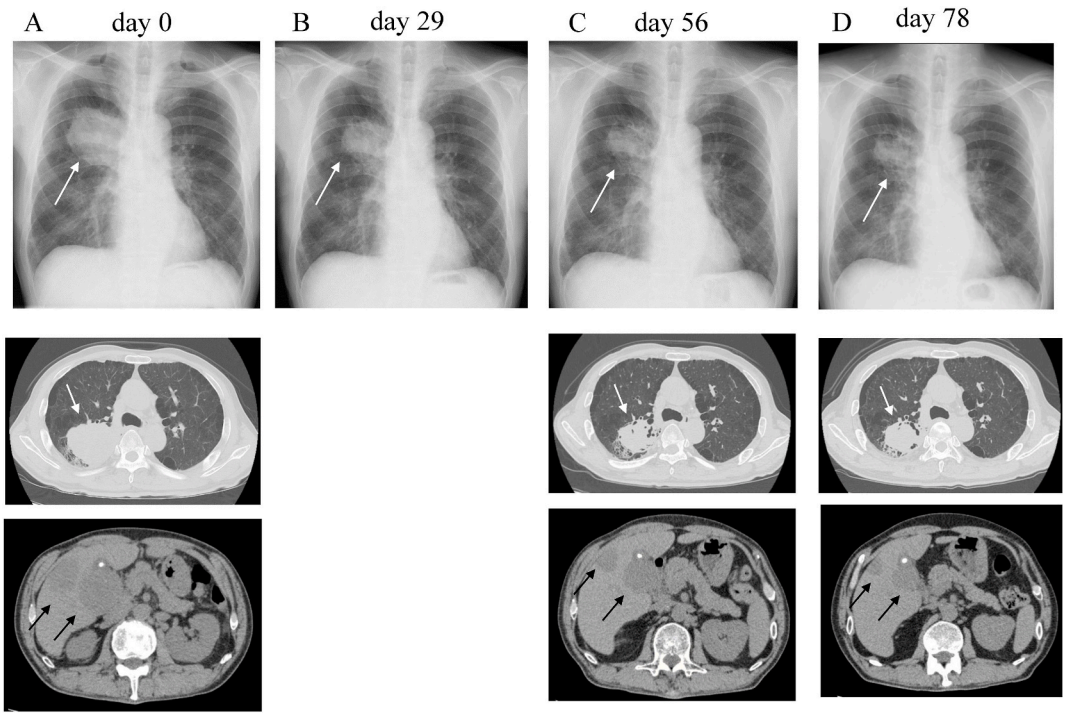

Fig. 2. Chest X-ray and computed tomography findings. On day 0 (A) before chemotherapy, there was a large nodule shadow (white arrows) in the right upper lobe and some low-density areas (arrows) in the liver. On days 29 (B), 56 (C), and 78 (D), the primary lesion (white arrows) and liver metastases (arrows) gradually shrank.

Table 2
Physical examination and function test results before and after anamorelin administration.

	Anamorelin (start from day 16)		
	Day 15 Before	Day 40 3 weeks later	Day 103 12 weeks later
BW (kg)	49.0	54.1[b]	59.7
BMI (kg/m^2)	17.4	19.2	21.2
Psoas muscle index (cm^2/m^2)	4.42[a]	–	5.12[c]
Lower leg circumference (cm)	29.8	31.3	34.3
SARC-F score	1	1	0
SPPB score	11	12	12
Handgrip strength (kg)	29.7	30.6	35.0
Gait speed (m/s)	1.34	1.40	1.38
Five times sit-to-stand test (s)	11.4	10.6	6.8

BMI, body mass index; BW, body weight; SARC-F, strength, assistant walking, rising from a chair, climbing stairs, and falls; SPPB: short physical performance battery.
[a] Day 7.
[b] Day 36.
[c] Day 92.

and quality of life. Here, a multimodal approach in addition to ANA administration was effective against CCX for improving not only appetite and BW but also physical functions.

4. Conclusion

1) In this case report, ANA showed sufficient appetite-enhancing and BW-gaining effects with excessive food intake. After a multidisciplinary collaborative approach to treatment was employed, worsening CCX rapidly improved with the recovery of physical function and increase in fat and PMI in a well-balanced manner while the patient with squamous NSCLC was on chemotherapy.
2) In Europe, ANA has not been approved because of its marginal effectiveness for improving LBM and ineffectiveness for improving handgrip strength and quality of life [21]. ANA alone would be less effective for CCX.
3) ANA administration, together with a multidisciplinary collaborative approach, can be an effective supportive therapy against worsening CCX in NSCLC patients undergoing chemotherapy.
4) In the future, prospective studies would be warranted involving treating CCX with ANA combined with a multidisciplinary collaborative approach.

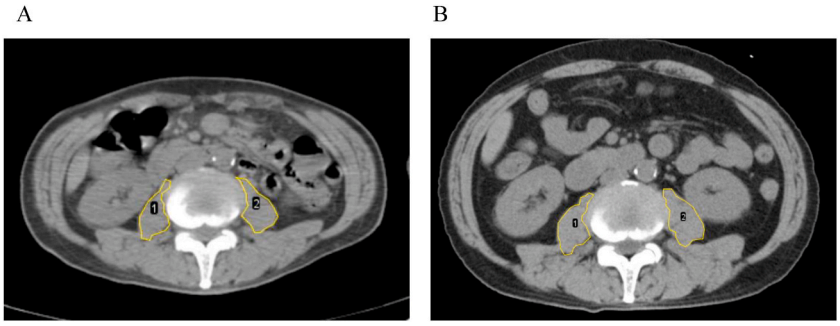

Fig. 3. Cross-sectional area (CSA, cm^2) of the psoas muscle at the caudal end of the L3 level on computed tomography. CSA was measured by manually tracing the boundaries of the right and left muscles, respectively. The total bilateral CSA was normalized for height (1.68 m) using the following equation: psoas muscle index (PMI, cm^2/m^2) = CSA of both psoas muscles (cm^2)/height^2 (m^2). Computed tomography on days −7 and 92 show PMIs of 4.42 cm^2/m^2 (A) and 5.12 cm^2/m^2 (B), respectively. Simultaneously, subcutaneous and visceral fat increased from day −7 to 92.

Author contributions

Y.O., K.M., and T.H. conceived the outline plan. All authors contributed to the data interpretation. F.Y. instructed the patient to self-exercise and measured his physical functions. M.N. performed nutrition counseling. All authors read and critically reviewed the manuscript draft and approved the final manuscript.

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Ethics approval and consent to participate

We obtained written informed consent from the patient to publish information, including laboratory data and image findings. This case report was approved by the institutional review board of Ishikiriseiki Hospital on August 25, 2021 (approval number: 21–27).

Declaration of competing interest

T.H. received research funding as a primary investigator from Ono Pharmaceutical Co., Ltd. (Osaka, Japan). The other authors declare no conflict of interest.

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