CANCER DIAGNOSIS & PROGNOSIS
2: 373-377 (2022) doi: 10.21873/cdp.10119

Body Weight Change in Non-small Cell Lung Cancer Patients Treated With EGFR-TKI

TAKAHIDE KODAMA[1], SHINYA SATO[1], KUNIHIKO MIYAZAKI[1], SHINICHIRO OKAUCHI[2], YUIKA SASATANI[2], GEN OHARA[2], KATSUNORI KAGOHASHI[2] and HIROAKI SATOH[2]

[1]*Division of Respiratory Medicine, Ryugasaki Saiseikai Hospital, Ryugasaki, Japan;*
[2]*Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba-Mito Kyodo General Hospital, Mito, Japan*

Abstract. *Background/Aim: Body weight (BW) changes in epidermal growth factor inhibitor-tyrosine kinase (EGFR-TKI) treated non-small cell lung cancer patients has yet to be fully investigated. For the purpose of clarifying changes in body weight in patients who received EGFR-TKI treatment in clinical practice, we performed a retrospective study. In this study, comparison between pretreatment BW and those at 12, 24 weeks, and 12 months in these patients was performed. Patients and Methods: We included all the patients diagnosed with EGFR mutated NSCLC in two tertiary hospitals between April 2009 and March 2021. BW records in the medical chart of each patient who was treated with EGFR-TKI for more than 12 weeks were surveyed. In each patient, BW at 12, 24 weeks, and 12 months from the initiation of EGFR-TKI treatment were compared with pretreatment BW. Results: Sixty-three patients obtained TKI treatment for more than 12 weeks and had comparable body weight records. Compared with the pretreatment BW, decreased BW was observed at 12, 24 weeks, and 12 months from the initiation of TKI treatment. Conclusion: Even in patients treated with EGFR-TKI, which is evaluated as less toxic and a more effective therapy, there might be patients who lose weight during the treatment period. Chest physicians will be required to provide medical care even for EGFR mutated patients, taking into consideration changes in BW.*

Correspondence to: Hiroaki Satoh, MD, Ph.D., Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba-Mito Kyodo General Hospital, 3-2-7 Miya-machi, Mito, Ibaraki, 310-0105, Japan. Tel: +81 292312371, e-mail: hirosato@md.tsukuba.ac.jp

Key Words: Body weight, epidermal growth factor inhibitor, tyrosine kinase, non-small cell lung cancer.

The use of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) is recommended by several guidelines as the first choice to control *EGFR* mutated non-small cell lung cancer (NSCLC) (1-3).

In clinical practice, EGFR-TKIs have been used for the long-term treatment of these patients (4). Recently, it has become possible to administer anamorelin, which is a novel selective ghrelin receptor agonist for cancer cachexia, and thus there is increasing interest in changes in body weight of cancer patients (5). Clinical trials on anamorelin included NSCLC patients receiving EGFR-TKIs (6-9). However, patients receiving EGFR-TKIs were less than 30 patients (9). In addition, these clinical trials observed changes in body weight from the start of anamorelin administration to 12 and 24 weeks (6-9), but did not investigate changes in body weight over a longer period of time. It was presumed that EGFR-TKI treatment, which has a high response rate, would not cause weight loss in patients; however, body weight change in NSCLC patients treated with EGFR-TKI has yet to be fully investigated.

For the purpose of clarifying changes in body weight in patients who received EGFR-TKI treatment in clinical practice, we performed a retrospective study. In this study, comparison between pretreatment body weight and those at 12, 24 weeks and 12 months in NSCLC patients treated with EGFR-TKIs was performed.

Patients and Methods

Patients. We analyzed the medical records of all patients diagnosed with *EGFR* mutated NSCLC in two tertiary hospitals in Japan (Ryugasaki Saiseikai Hospital and Mito Medical Center, University of Tsukuba) between April 2009 and March 2021. NSCLC was diagnosed based on the World Health Organization classification. Tumor-node-

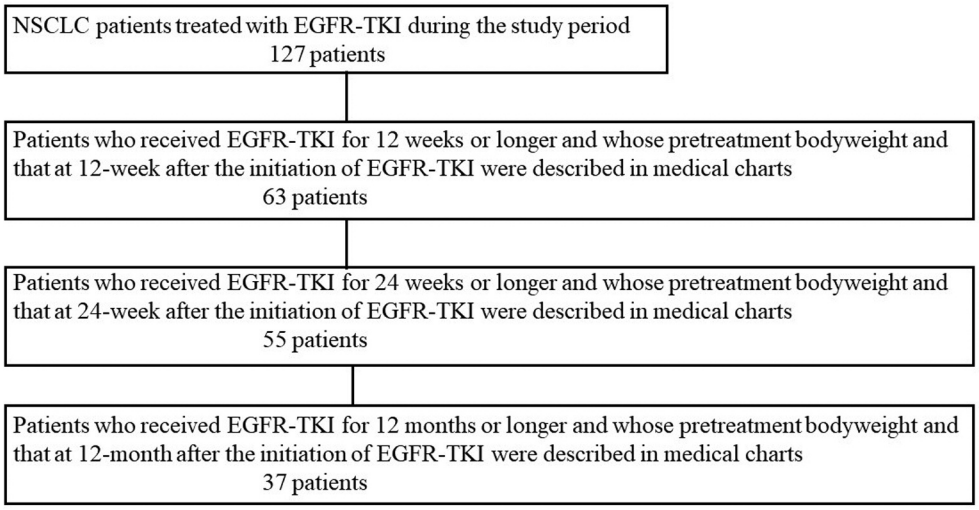

Figure 1. *Study flow chart*.

metastasis staging (TNM Classification, 8th edition) using head computed tomography or magnetic resonance imaging, bone scans, and ultrasonography and/or computed tomography of the abdomen was performed in all patients prior to EGFR-TKI therapy initiation. Patients with the following comorbidities and with a history of treatment for these conditions were excluded: parasitic infestations, allergic diseases, auto-immune diseases, and hematologic malignancies. Patients with chronic obstructive pulmonary disease and those with bronchial asthma and chronic obstructive pulmonary disease overlap requiring systemic steroid use were also excluded. Patient demographic data including age, sex, Eastern Cooperative Oncology Group score for performance status, histopathology, disease stage, objective tumor response, and duration of TKI therapy were obtained from the patients' medical charts.

Statistical analysis. For each patient, pretreatment body weight was compared with that at 12, 24 weeks, and 12 months after the initiation of EGFR-TKI therapy using Wilcoxon signed-rank test. To compare the different groups of patients, the chi-square test was also used. All statistical analyses were performed using SPSS software, version 10.1 for Windows (SPSS Inc., Chicago, IL, USA) and $p<0.05$ was considered to indicate a statistically significant difference.

Ethics. This study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent for a non-interventional retrospective study was obtained from each patient. The analysis of the medical records of patients with lung cancer was approved by the ethics committee of Mito Medical Center, University of Tsukuba (NO 20-57).

Results

Patient characteristics. Figure 1 shows the study flow chart. During the study period, 127 NSCLC patients were treated with EGFR-TKI. Among them, 63 patients who received EGFR-TKI for 12 weeks or longer and whose pretreatment bodyweight and that at 12-weeks after the initiation of EGFR-TKI were described in medical charts. Among the 63 patients, 24 were male, and their median age was 72 years (range=46-92 years). Sixty patients had adenocarcinoma, two had adenosquamous cell cancer, and one had squamous cell cancer. Seventeen patients had stage IIIA-C and 46 had stage IVA-B. Regarding *EGFR* mutations, 45 patients had Ex19 deletion, 15 had Exon 21 L858R, and 3 had others. Regarding the therapeutic effect of EGFR-TKI, since the 63 patients received TKI for 12 weeks or longer, 61 patients were evaluated as 'partial response', and 2 had 'stable disease'.

Bodyweight change during EGFR-TKI in each patient. Focusing on each patient, the changes in body weight before and at 12, 24 weeks, and 12 months after the initiation of TKI are shown in Table I. At 12, 24 weeks, and 12 months after the initiation of treatment, body weight in each patient was reduced (Wilcoxon signed-rank test).

Table II shows changes in body weight in two age groups: patients younger than 70 years old and those 70 years or older. In both age groups, body weight was reduced at 12 weeks and 12 months. Table III shows changes in body weight in male and female patients. In male patients, the decrease in body weight was significant at 12 weeks, but the change was not statistically significant at 24 weeks and at 12 months. On the other hand, a decrease in body weight was found at 12, 24 weeks, and 12 months in female patients.

Table IV shows changes in body weight according to pretreatment body weight. In patients whose pretreatment body weight was less than 40 kg, no statistically significant decrease in body weight was found at 12, 24 weeks, and 12 months. Significant decrease in body weight was found only

Table I. *Changes in body weight in all the 63 patients.*

	No. of patients	BW: median (range)	*p*-Value*
Pretreatment BW	63	53.1 (33.9-80.0)	
BW at 12 weeks	63	50.0 (34.8-80.5)	0.0003
BW at 24 weeks	55	50.0 (31.0-81.0)	0.0135
BW at 12 months	37	50.0 (31.2-80.5)	0.1018

BW: Body weight. *Comparison with pretreatment weight of each patient (Wilcoxon signed-rank test).

Table II. *Changes in body weight by age.*

Age group	No. of patients	BW: median (range)	*p*-Value*
Less than 70 years old			
Pretreatment BW	26	53.4 (40.9-71.3)	
BW at 12 weeks	26	50.5 (36.0-67.0)	0.0216
BW at 24 weeks	21	51.8 (38.0-63.1)	0.0604
BW at 12 months	16	50.0 (35.9-63.1)	0.0267
70 years old or more			
Pretreatment BW	37	51.8 (33.9-80.0)	
BW at 12 weeks	37	49.5 (34.8-80.5)	0.0049
BW at 24 weeks	34	48.4 (31.0-81.0)	0.0855
BW at 12 months	21	48.0 (31.2-80.5)	0.0255

BW: Body weight. *Comparison with pretreatment weight of each patient (Wilcoxon signed-rank test).

Table III. *Changes in body weight by sex.*

Sex	No. of patients	BW: median (range)	*p*-Value*
Male			
Pretreatment BW	24	60.0 (38.8-80.0)	
BW at 12 weeks	24	59.4 (41.3-80.5)	0.0431
BW at 24 weeks	19	58.0 (41.5-81.0)	0.4348
BW at 12 months	12	59.1 (42.8-80.5)	0.9645
Female			
Pretreatment BW	39	49.2 (33.9-70.7)	
BW at 12 weeks	39	48.1 (34.8-68.6)	0.0014
BW at 24 weeks	36	48.2 (31.0-67.8)	0.0219
BW at 12 months	25	46.6 (31.0-66.0)	0.0005

BW: Body weight. *Comparison with pretreatment weight of each patient (Wilcoxon signed-rank test).

Table IV. *Changes in body weight by pretreatment body weight.*

BW group	No. of patients	BW: median (range)	*p*-Value*
Less than 40 kg			
Pretreatment BW	6	36.6 (33.9-38.8)	
BW at 12 weeks	6	36.5 (34.8-41.3)	0.4004
BW at 24 weeks	6	34.7 (31.0-41.5)	0.7150
BW at 12 months	4	35.0 (31.2-36.6)	0.7150
40 kg-less than 50 kg			
Pretreatment BW	19	43.0 (40.3-49.6)	
BW at 12 weeks	19	43.2 (36.0-51.0)	0.1023
BW at 24 weeks	17	43.2 (35.0-66.0)	0.7332
BW at 12 months	11	42.8 (35.0-48.5)	0.0125
50 kg-less than 60 kg			
Pretreatment BW	21	54.3 (50.0-59.9)	
BW at 12 weeks	21	53.1 (46.0-59.5)	0.0102
BW at 24 weeks	19	53.3 (45.0-63.0)	0.1639
BW at 12 months	13	50.1 (45.0-56.1)	0.0280
60 kg or more			
Pretreatment BW	17	65.2 (60.0-80.0)	
BW at 12 weeks	17	63.6 (59.2-80.5)	0.0105
BW at 24 weeks	13	64.6 (43.0-81.0)	0.0229
BW at 12 months	9	63.1 (54.7-80.5)	0.3270

BW: Body weight. *Comparison with pretreatment weight of each patient (Wilcoxon signed-rank test).

at 12 months in patients whose pretreatment body weight was 40-49 kg. In patients whose pretreatment body weight was 50-59 kg, the decrease in body weight was significant at 12 weeks and 12 months. The decrease in body weight was significant at 12 weeks and 24 weeks in patients whose pretreatment body weight was 60 kg or more.

Discussion

Compared to cytotoxic chemotherapeutic agents, EGFR-TKIs have controllable adverse effects (AEs) except for the drug-induced lung injury (10-13). Although some EGFR-TKIs cause skin and gastroenterological AEs, standard treatment methods have been established (10-13). It is generally recognized that EGFR-TKIs are less toxic drugs (10-13). On the other hand, in terms of efficacy, it is known that the response rates are higher and the response periods are longer than those of cytotoxic agents (4). Therefore, EGF-TKIs are considered to be 'more effective' and 'less toxic' drugs. Taking these into consideration, we speculated that weight loss in patients receiving TKI treatment would be limited. To our best knowledge, we could not find any reports examining changes in body weight during administration of EGFR-TKIs to NSCLC patients. Therefore, this is the first study to investigate short-term and long-term weight changes in these patients. The results of the present study showed that weight loss is observed not only short-term, but also long-term. Weight loss in underweight patients and elderly patients was concerned about, but the results were not. Although the reason could not be clarified, the persistence of weight loss in women was significant.

It is possible that the weight loss observed in the present study is within the range of natural weight fluctuations (14-16). In general, "weight loss of 5% or more in 6 months" is often regarded as 'weight loss due to pathological condition' or 'cachexia' (16). The median pretreatment body weight of the 63 patients included in this study was 53.1 kg, with a 5% weight loss of 2.7 kg. As shown in Table I, the difference between the median body weight before treatment and after 12 weeks, 24 weeks, and 12 months was 3.1 kg, respectively. The difference between pretreatment and 12 and 24 weeks was statistically significant, but its interpretation might be controversial. However, considering that the results of the study were obtained from patients who received TKI for 12 weeks or more with 96.8% PR. The weight loss of patients treated with EGFR-TKIs, who had a high response rate and few serious side effects, was impressive.

Clinical trials on anamorelin evaluated patients after only 12 and 24 weeks of administration, whereas those on EGFR-TKI evaluated patients also after one year of treatment. Therefore, it is suggested that the weight evaluation period of anamorelin was short. In a Japanese subgroup analysis of the LUX-Lung-3 trial, median PFS for afatinib was 13.8 months (17). In the FLAURA study Japanese subgroup analysis, the median PFS of the osimertinib group was 19.1 months (18). Considering these results, it might be necessary to evaluate long-term weight changes in NSCLC patients receiving EGR-TKI treatment. Studies on body weight changes associated with long-term administration of anamorelin should be conducted in many study groups. From the viewpoint of comparison of such studies, the results of the present study might be considered to be significant.

Although the results were considered to be significant, there were some limitations to the present study. First, the study was retrospective and included a small number of patients. The number of patients whom body weight changes were described was about half of the patients who were actually receiving TKI. In contrast to the results of clinical trials on anamorelin, our study was conducted on patients who received TKI for 12 weeks or longer. However, it is arguable whether this was an appropriate inclusion criterium. It might also have needed more discussion about which time points are appropriate for assessing weight changes. The results need to be validated in a statistically well-planned prospective clinical trial with a large number of patients.

The purpose of this study was to clarify the body weight changes in EGFR-TKI-administered patients in clinical practice. However, it is known that EGFR-TKI treatment is effective in the majority of patients and has a long response period. Given these circumstances, it was speculated that there would be no significant weight loss with this treatment, however, the results were different. Our results suggest that nutrition and weight management are important even for patients receiving EGFR-TKI treatment. Since anamorelin is now administered, it is speculated that anamorelin administration is also useful as a countermeasure against emaciation, even in EGFR-TKI-treated patients. Chest physicians will be required to provide medical care even for *EGFR* mutated patients, taking into consideration the changes in body weight.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Collecting data: TK, SS, KM, SO, YS, GO, KK, and HS. Statistical analysis: TK, KM, and HS. Writing manuscript: TK, KM, and HS. Supervision: HS. All Authors have read and agreed to the published version of the manuscript.

References

1 Hanna N, Johnson D, Temin S and Masters G: Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update summary. J Oncol Pract *13(12)*: 832-837, 2017. PMID: 28850309. DOI: 10.1200/JOP.2017.026716

2 NCCN Guidelines for non-small cell lung cancer. Updates in Version 2. 2020 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 1. 2020. NSCL-18 Available at: https://www2.tri-kobe.org/nccn/guideline/lung/english/non_small.pdf [Last accessed on March 2, 2022]

3 Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, Reck M, Smit EF, Syrigos K, Stahel R, Felip E, Peters S, Panel Members. and ESMO: 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol *25(8)*: 1475-1484, 2014. PMID: 24669016. DOI: 10.1093/annonc/mdu123

4 Greenhalgh J, Dwan K, Boland A, Bates V, Vecchio F, Dundar Y, Jain P and Green JA: First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev *(5)*: CD010383, 2016. PMID: 27223332. DOI: 10.1002/14651858.CD010383.pub2

5 Fonseca GWPD and von Haehling S: An overview of anamorelin as a treatment option for cancer-associated anorexia and cachexia. Expert Opin Pharmacother *22(7)*: 889-895, 2021. PMID: 33491505. DOI: 10.1080/14656566.2021.1873954

6 Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y and Fearon KC: Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol *17(4)*: 519-531, 2016. PMID: 26906526. DOI: 10.1016/S1470-2045(15)00558-6

7 Takayama K, Katakami N, Yokoyama T, Atagi S, Yoshimori K, Kagamu H, Saito H, Takiguchi Y, Aoe K, Koyama A, Komura N and Eguchi K: Anamorelin (ONO-7643) in Japanese patients with non-small cell lung cancer and cachexia: results of a randomized phase 2 trial. Support Care Cancer *24(8)*: 3495-3505, 2016. PMID: 27005463. DOI: 10.1007/s00520-016-3144-z

8 Currow D, Temel JS, Abernethy A, Milanowski J, Friend J and Fearon KC: ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. Ann Oncol *28(8)*: 1949-1956, 2017. PMID: 28472437. DOI: 10.1093/annonc/mdx192

9 Katakami N, Uchino J, Yokoyama T, Naito T, Kondo M, Yamada K, Kitajima H, Yoshimori K, Sato K, Saito H, Aoe K, Tsuji T, Takiguchi Y, Takayama K, Komura N, Takiguchi T and Eguchi K: Anamorelin (ONO-7643) for the treatment of patients with non-small cell lung cancer and cachexia: Results from a randomized, double-blind, placebo-controlled, multicenter study of Japanese patients (ONO-7643-04). Cancer *124(3)*: 606-616, 2018. PMID: 29205286. DOI: 10.1002/cncr.31128

10 Remon J, Morán T, Reguart N, Majem M, Carcereny E and Lianes P: Beyond EGFR TKI in EGFR-mutant non-small cell lung cancer patients: main challenges still to be overcome. Cancer Treat Rev *40(6)*: 723-729, 2014. PMID: 24759598. DOI: 10.1016/j.ctrv.2014.03.006

11 Long K and Suresh K: Pulmonary toxicity of systemic lung cancer therapy. Respirology *25(Suppl 2)*: 72-79, 2020. PMID: 32729207. DOI: 10.1111/resp.13915

12 Hsu WH, Yang JC, Mok TS and Loong HH: Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol *29(suppl_1)*: i3-i9, 2018. PMID: 29462253. DOI: 10.1093/annonc/mdx702

13 Aw DC, Tan EH, Chin TM, Lim HL, Lee HY and Soo RA: Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. Asia Pac J Clin Oncol *14(1)*: 23-31, 2018. PMID: 28464435. DOI: 10.1111/ajco.12687

14 Soenen S and Chapman IM: Body weight, anorexia, and undernutrition in older people. J Am Med Dir Assoc *14(9)*: 642-648, 2013. PMID: 23522494. DOI: 10.1016/j.jamda.2013.02.004

15 Wysokiński A, Sobów T, Kłoszewska I and Kostka T: Mechanisms of the anorexia of aging-a review. Age (Dordr) *37(4)*: 9821, 2015. PMID: 26232135. DOI: 10.1007/s11357-015-9821-x

16 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M and European Working Group on Sarcopenia in Older People: Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing *39(4)*: 412-423, 2010. PMID: 20392703. DOI: 10.1093/ageing/afq034

17 Kato T, Yoshioka H, Okamoto I, Yokoyama A, Hida T, Seto T, Kiura K, Massey D, Seki Y and Yamamoto N: Afatinib versus cisplatin plus pemetrexed in Japanese patients with advanced non-small cell lung cancer harboring activating EGFR mutations: Subgroup analysis of LUX-Lung 3. Cancer Sci *106(9)*: 1202-1211, 2015. PMID: 26094656. DOI: 10.1111/cas.12723

18 Ito K, Morise M, Wakuda K, Hataji O, Shimokawaji T, Takahashi K, Furuya N, Takeyama Y, Goto Y, Abe T, Kato T, Ozone S, Ikeda S, Kogure Y, Yokoyama T, Kimura M, Yoshioka H, Murotani K, Kondo M and Saka H: A multicenter cohort study of osimertinib compared with afatinib as first-line treatment for EGFR-mutated non-small-cell lung cancer from practical dataset: CJLSG1903. ESMO Open *6(3)*: 100115, 2021. PMID: 33984681. DOI: 10.1016/j.esmoop.2021.100115

Received February 8, 2022
Revised March 1, 2022
Accepted March 2, 2022