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ORIGINAL ARTICLE

Differences in skeletal muscle loss caused by cytotoxic chemotherapy and molecular targeted therapy in patients with advanced non-small cell lung cancer

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Abstract

Background: Recent studies have revealed a reduction in the skeletal muscle area in patients with advanced non-small cell lung cancer (NSCLC) after chemotherapy. EGFR and ALK tyrosine kinase inhibitor (TKI)-based therapies are less cytotoxic than chemotherapy, but differences in skeletal muscle mass between patients receiving EGFR and ALK TKI therapies and patients receiving cytotoxic chemotherapy have not yet been reported.

Methods: Data of pathologically proven NSCLC patients were reviewed, and chest computed tomography and/or positron emission tomography-computed tomography images obtained from January 2012 to December 2014 were selected. Patients were divided into two groups: cytotoxic chemotherapy (CG) and molecular targeted (MG). Muscle mass was measured with a single cross-sectional area of the muscle at the third lumber vertebra (L3MA). To estimate skeletal muscle changes during chemotherapy, we defined the following L3 skeletal muscle index (L3SMI) ratio: post L3SMI/pre L3SMI. Differences in the SMI ratio between the groups were evaluated using the Wilcoxon signed-rank test.

Results: Sixty-five patients were included in this study: 44 patients received cytotoxic chemotherapy and 21 received molecular targeted therapy (EGFR and ALK TKI). The loss of L3MA in the CG was higher than in the MG ($P = 0.03$). In the CG, the L3SMI ratio defined to evaluate skeletal muscle mass changes was significantly lower than in the MG ($P = 0.0188$).

Conclusion: Our results suggest that skeletal muscle loss during first-line therapy was significantly different between patients receiving cytotoxic chemotherapy and those receiving TKIs. Specifically, skeletal muscle loss was lower in patients receiving TKIs than in patients receiving cytotoxic chemotherapy.

Introduction

Non-small cell lung cancer (NSCLC) is the most common lung cancer and has the highest incidence in men and the third highest in women. Moreover, NSCLC is the most common cause of cancer-related death in men and the second in women.[1,2]

Patients with NSCLC usually progress to advanced stages of the disease, at which time chemotherapy is recommended. Personalized strategies based on molecular subtypes, such as the presence of *EGFR*, *ALK*, and *ROS1* gene mutations, have improved chemotherapy. In appropriately selected patients, EGFR-tyrosine kinase inhibitors (EGFR-TKIs) and ALK-TKIs can significantly improve progression-free survival and are less cytotoxic than chemotherapy.[3,4]

Cancer cachexia is a common feature of advanced lung cancer and is defined as a multifactorial syndrome of progressive weight loss, anorexia, and skeletal muscle mass (SMM) loss in response to a malignant growth.[5,6] Sarcopenia, which is characterized by a progressive, generalized loss of SMM and is a predictor of poor outcomes, is recognized as a central component of cancer cachexia syndrome

in oncologic patients.[7] Sarcopenia is associated with an increase in adverse events of cancer treatment and poor survival in several cancers, such as breast, gastrointestinal tract, and lung cancers.[6,8–12]

Computed tomography (CT) image analyses can be used to measure muscle mass.[13]

The quantification of SMM is important to evaluate sarcopenia. Sarcopenia is defined as muscle depletion and the criterion is two standard deviations below the mean of a young reference group. A single cross-sectional area of SMM at the third lumbar vertebra level was found to correlate best with the total body SMM in patients with cancer.[14–17] Thus, a single cross-sectional measurement of muscle at the third lumbar vertebra is the gold standard for estimating SMM.

Chemotherapy improves quality of life (QOL) and survival in patients with advanced cancer, but knowledge regarding changes in SMM is limited and results are conflicting.[17,18] In some studies, patients with cancer who underwent cytotoxic chemotherapy lost muscle mass; however, in other studies, patients gained muscle mass.[18–20] Recent studies have revealed a reduction in the skeletal muscle area (SMA) in patients with advanced NSCLC after cytotoxic chemotherapy.[21] EGFR and ALK TKI-based therapies are known to be less cytotoxic than chemotherapy, except in interstitial lung disease; however, to the best of our knowledge, SMM differences in patients receiving molecular targeted anti-tumor agents and those receiving cytotoxic chemotherapy have not yet been reported.[3,4]

Thus, this study aimed to evaluate the loss in SMA before and after therapy in patients receiving cytotoxic chemotherapy and patients receiving EGFR or ALK TKI-based therapy.

Methods

Patients

The medical records of patients with pathologically proven NSCLC were reviewed, and chest computed tomography (CT) and positron emission tomography (PET)-CT images obtained from January 2012 to December 2014 at the St. Marianna University School of Medicine Hospital were selected.

The inclusion criteria were as follows: pathologically confirmed stage IV NSCLC according to the Union for International Cancer Control tumor node metastasis (TNM) stage classification, the administration of first-line chemotherapy, and CT images (coverage of L2/L3 vertebral bodies) before and after therapy.

Patients were divided into two groups: cytotoxic chemotherapy (CG) and molecular targeted (MG).

This retrospective study was approved by the Institutional Review Board of St. Marianna University School of Medicine, which waived the need for informed patient consent (reference number 3619).

Computed tomography imaging to measure skeletal muscle mass (SMM)

All patients were scanned with a 64-row or 80-row detector CT scanner (Aquilion 64 or Aquilion PRIME, Toshiba Medical Systems, Otawara, Tochigi, Japan) or a 16-row detector PET-CT scanner (TruePoint Biograph16 or Biograph Horizon, Siemens, Knoxville, TN, USA) before and after chemotherapy.

Muscle mass was measured based on a single cross-sectional scan of the muscle area at the third lumbar vertebra (L3MA). The L3MA measurements for this study were performed using ImageJ software, a semiautomatic threshold technique to isolate the tissue from other tissues and structures, from the National Institutes of Health (ImageJ, version 1.50, NIH, Bethesda, MD, USA, http://imagej.nih.gov/ij/), according to previously described methods.[22]

ImageJ can analyze a single cross-sectional CT image at adequate attenuation values (Hounsfield Unit, HU) and accurately measure the cross-sectional area (mm^2). Figure 1 describes the method used to calculate the L3MA. First, we opened the DICOM image in ImageJ and made adjustments to allow the anatomical features at L3 to be easily distinguished (Fig 1a). We then traced the outer perimeter of the abdominal musculature and measured the cross-sectional area (measurement 1, Fig 1b).

Subsequently, we adjusted the lower and upper threshold to −250 HU to trace the inner perimeter of the abdominal musculature and measure the area of the inner perimeter (measurement 2, Fig 1c). Finally, the L3MA (cm^2) was calculated as follows: (*measurement 1 − measurement 2 = measurement 3) measurement 3/100.* The L3 skeletal muscle index (*L3SMI; L3MA/height*^{2}) was used to determine sarcopenia.

We estimated skeletal muscle changes during chemotherapy based on the L3SMI ratio (*post-L3SMI/preL3SMI*). Specifically, sarcopenia was defined as an L3SMI <49 cm^2/m^2 for men and <31 cm^2/m^2 for women based on a Korean study of Asian populations.[9]

Statistical analysis

The differences between CG and MG were evaluated using the Wilcoxon signed-rank test. For categorical variables, comparisons between subjects were performed using chi-squared or Fisher's exact tests. Continuous variables were compared using the Student's *t* or Wilcoxon signed-rank tests. All statistical analyses were performed using JMP Pro

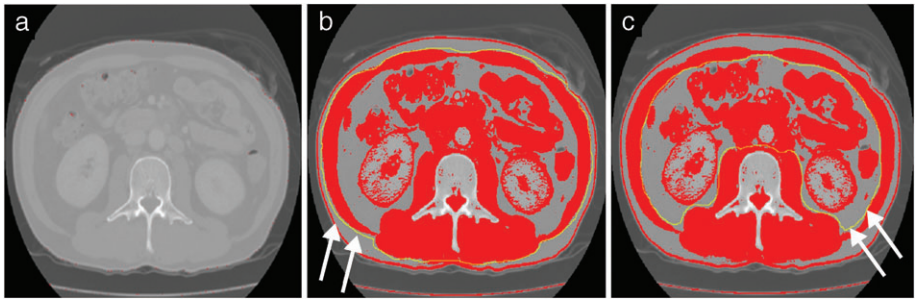

Figure 1 Method for measuring the third lumber muscle mass area using ImageJ. (**a**) The initial computed tomography image was adjusted to the lower and upper thresholds of –250 Hounsfield units (HU) to allow the anatomical features at L3 to be easily distinguished. (**b**) The outer abdominal musculature was delineated and the muscle mass area was measured (measurement 1), with the lower and upper thresholds to –29 and 150 HU. (**c**) The inner abdominal musculature was delineated and the muscle mass area was measured (measurement 2), with the lower and upper thresholds to –29 and 150 HU. The arrows indicate the tracing lines (yellow line).

12.0 software (SAS Institute, Cary, NC, USA). For all statistical analyses, $P < 0.05$ was considered significant.

Results

Patient characteristics

The CT scans of 118 patients from January 2012 to December 2014 were reviewed and 65 were selected. Patients were excluded if they lacked or had unclear CT images (L2/L3 vertebral bodies) before or after chemotherapy, if they discontinued chemotherapy, or if they died. The mean time between pretreatment to post-treatment CT was 132 days. There was no significant difference in the time from pretreatment to post-treatment CT between the groups (CG 125.2 vs. MG 131.4 days; $P = 0.57$).

Patient characteristics are summarized in Table 1. Of the 65 patients, 44 received cytotoxic chemotherapy and 21 received molecular targeted therapy (EGFR or ALK TKI). In both groups, adenocarcinoma was the most common histologic type (51 patients, 78.5%), and the most common performance status (PS) ranged from 0 to 1 (51 patients, 78.4%). There were more women in the MG than in the CG (57.1% and 29.3%, respectively; $P = 0.0325$). Adenocarcinoma and *EGFR* mutations were more prevalent in the MG than in the CG (adenocarcinoma 100.0% vs. 68.2%, respectively, $P = 0.0142$; *EGFR* mutant 90.5% vs. 4.6%, respectively, $P < 0.0001$). The incidence of sarcopenia (MG 28.6% vs. CG 45.5%; $P = 0.1938$), age, and PS did not significantly differ between the groups.

Chemotherapy regimen and response assessment

The chemotherapy regimens and treatment responses are summarized in Table 2. All patients received first-line chemotherapy. Forty-three patients received platinum-based combination therapy, including carboplatin (CBDCA) + pemetrexed (PEM) ± bevacizumab (Bev); cisplatin (CDDP) + PEM ± Bev; CBDCA + gemcitabine (GEM); CDDP + GEM; CBDCA + paclitaxel (PTX); CBDCA + nab-PTX; and CDDP + docetaxel (DTX). One patient received single-agent chemotherapy (PEM), and 21 patients received molecular targeted therapy, including gefitinib, erlotinib, afatinib, crizotinib, and alectinib. MG was associated with a higher objective response rate (57.1% vs. 29.5%; $P = 0.0036$).

Changes in skeletal muscle mass (SMM) and differences in between groups

Table 3 shows the SMM measurements and the differences between treatments. In all patients, the mean SMM significantly decreased from 114.58 cm^2 before chemotherapy to 105.6 cm^2 after chemotherapy ($P < 0.001$), corresponding to a mean SMM change of 9.0 cm^2. Furthermore, the SMM was significantly reduced in each group (CG $P < 0.001$; MG $P = 0.0032$), and the reduction in L3MA was greater in the CG than in the MG ($P = 0.0262$). Figure 2 shows the significant differences in the L3SMI ratios between the groups.

Discussion

In this study, we investigated the differences in SMA in patients with advanced NSCLC before and after chemotherapy. The reduction in skeletal muscle during first-line chemotherapy significantly differed between patients receiving EGFR or ALK TKI (MG) and patients receiving cytotoxic chemotherapy (CG). Skeletal muscle loss was lower in the MG than in the CG. To best of our knowledge, this study is the first to demonstrate significant differences in the loss of skeletal muscle in NSCLC patients receiving molecular targeted therapy or cytotoxic chemotherapy.

Table 1 Patient characteristics

Characteristics	All patients (n = 65)	Cytotoxic chemotherapy group (n = 44)	Molecular targeted therapy group (n = 21)	P
Age, mean ± SD	66.0 ± 10.5	67.2 ± 7.7	63.3 ± 14.6	0.5228
Gender, N (%)				
Female	25 (38.5)	13 (29.6)	12 (57.1)	0.0325
Male	40 (61.5)	31 (70.5)	9 (42.9)	
Height (cm), mean ± SD	160.8 ± 9.9	161.4 ± 9.3	160.0 ± 11.1	0.4397
Baseline weight (kg), mean ± SD	56.8 ± 11.2	56.3 ± 10.6	57.8 ± 12.4	0.5652
BMI	21.9 ± 3.2	21.7 ± 3.4	22.4 + 3.0	0.373
ECOG PS, N (%)				
0	16 (24.6)	12 (24.27)	4 (19.1)	0.7167
1	35 (53.8)	22 (50.0)	13 (61.9)	
2	9 (13.8)	7 (15.9)	2 (9.5)	
3	5 (7.7)	3 (6.8)	2 (9.5)	
Sarcopenia	26 (40.0)	20 (45.5)	6 (28.6)	0.1938
Tumor histology, N (%)				
Adenocarcinoma	51 (78.5)	30 (68.2)	21 (100.0)	0.0142
Squamous	8 (12.3)	8 (18.2)	0 (0.0)	
Non-small cell carcinoma	6 (9.2)	6 (13.6)	0 (0.0)	
Mutations, N (%)				
EGFR gene mutant	21 (32.3)	2 (4.6)	19 (90.5)	<0.0001
ALK fusion gene	3 (4.6)	1 (2.3)	2 (9.5)	
Wild type	41 (63.0)	41 (93.1)	0 (0.0)	
Albumin (g/dL), mean ± SD	3.8 ± 0.5	3.7 ± 0.5	3.9 ± 0.5	0.2021
CRP (mg/dL), mean ± SD	2.5 ± 3.2	2.9 ± 3.6	1.4 ± 1.8	0.1226
LDH (IU/l), mean ± SD	256.0 ± 162.0	247.8 ± 120.0	273 ± 230.0	0.7736

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

Table 2 Chemotherapy regimen and response evaluation

Regimen/Response	All patients (n = 65)	Cytotoxic chemotherapy group (n = 44)	Molecular targeted therapy group (n = 21)	P
Chemotherapy regimen, N (%)				< 0.001
Platinum-based combination	43 (66.2)	43 (97.7)	0 (0.0)	
Single agent (cytotoxic drug)	1 (1.5)	1 (2.3)	0 (0.0)	
Single agent (*EGFR*-TKI or *ALK*-TKI)	21 (32.3)	0 (0.0)	21 (100.0)	
Treatment response, N (%)†				0.0036
Partial response	25 (38.5)	13 (29.5)	12 (57.1)	
Stable disease	29 (44.6)	20 (45.5)	9 (42.9)	
Progressive disease	11 (16.9)	11 (25.0)	0 (0)	

†Response Evaluation Criteria in Solid Tumors version 1.1. TKI, tyrosine kinase inhibitor.

The mean SMA was significantly decreased in both groups. Notably, multiple factors are responsible for skeletal muscle loss in advanced lung cancer. Underlying malignancy and cachexia can reduce patient activity and food intake, as well as cause metabolic dysfunctions (e.g. proteolysis, lipolysis, and insulin resistance). These effects can exacerbate the loss of SMM and body weight in patients with cancer. Although chemotherapy can prevent the loss of SMM in some patients, it is known to reduce SMM in most patients.[21,23]

Little is known regarding the specific reasons why patients receiving chemotherapy either maintain or gain SMM, but we hypothesized that the decreases in SMM would differ between CG and MG. We attributed these differences to adverse events during treatment, such as fatigue, loss of appetite, nausea, vomiting, and diarrhea. These side effects can negatively affect food intake, physical activity and the overall QOL of patients, contributing to an aggressive loss of SMM. Molecular targeted therapy is less toxic than cytotoxic chemotherapy;[3,4] therefore, the differences in adverse events during treatment may affect the SMM reduction rate. Moreover, these differences may also be attributed to differences in tumor response rates during treatment. Similar to previous studies, we showed large variations in the changes in SMM during cytotoxic chemotherapy (Table. 3).[21] Some patients

Table 3 Measurement of skeletal muscle mass and L3 skeletal muscle index ratio before and after chemotherapy

Measurement	All patients (n = 65)	Cytotoxic chemotherapy group (n = 44)	Molecular targeted therapy group (n = 21)	P
Pre L3 SMA (cm^2) mean SE	114.58 (3.1)*	117.0 (3.6)**	109.5 (6.0)***	0.1427
Pre L3 SMI (cm^2/m^2) mean SE	44.0 (0.9)	44.8 (1.1)	42.5 (1.5)	0.2043
Post L3 SMA (cm^2) mean SE	105.6 (2.7)*	105.5 (3.0)**	105.9 (5.5)***	0.7049
Post L3 SMI (cm^2/m^2) mean SE	40.7 (0.8)	40.4 (1.0)	41.1 (1.3)	0.4615
Difference in pre-SMA to post-SMA (cm^2) mean SE	9.0 (1.6)	11.5 (2.2)	3.6 (1.6)	0.0262
L3 SMI ratio mean SE	0.93 (0.01)	0.91 (0.02)	0.97 (0.01)	0.0188

*P < 0.001, **P < 0.001, ***P = 0.00332. L3SMI, third lumbar skeletal muscle index; L3 SMI ratio, post-L3SMI/preL3SMI; SE, standard error; SMA, skeletal muscle area.

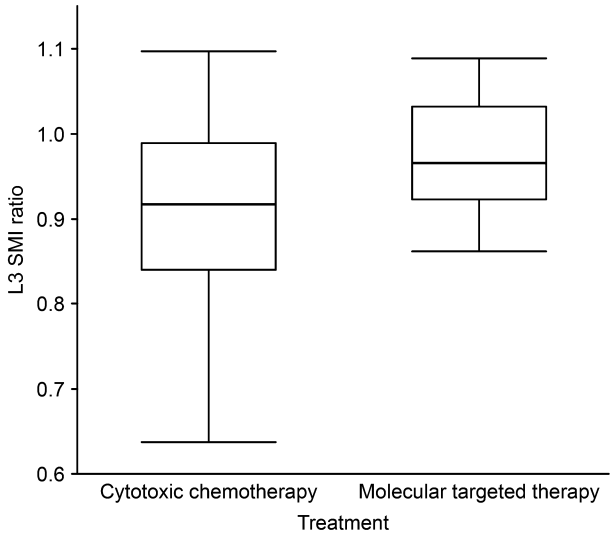

Figure 2 Third lumbar skeletal muscle index (L3SMI) ratio differences between groups receiving cytotoxic chemotherapy or molecular targeted therapy (n = 65; P = 0.0188). L3SMI ratio: post-L3 SMI/preL3 SMI.

maintained or increased their muscle mass, whereas others showed a decrease after chemotherapy. Stene *et al.* reported that skeletal muscle changes tended to depend on the response of the tumor to chemotherapy and suggested that chemotherapy might prevent catabolic processes that drive muscle breakdown. In general, molecular targeted therapy in advanced lung cancer is superior to cytotoxic therapy, and the guidelines recommend that patients who can receive molecular targeted therapy should be treated with these drugs first.[24] In this study, the response rate to chemotherapy was similar to response rates in previous studies of NSCLC patients.[3,4,25] Although the tumor response rate to chemotherapy was not significantly associated with the L3SMI ratio in this study, the tumor response in the MG was superior to the CG. Moreover, differences in the SMM may have been the result of gender differences between the groups. Men reportedly experience significantly larger decreases in SMM during chemotherapy, and these decreases follow a hyperbolic pattern (i.e. the rate of reduction and the amount of muscle tissue exhibited a hyperbolic relationship).[17] Moreover, *EGFR* mutations are more common in women, which may have affected the results of the MG in our study because it contained more women.

This study has several limitations that should be noted. First, this study was retrospective with a small sample size and was conducted at a single institution. Our observations should be reproduced in additional multi-center studies with patients with advanced lung cancer. Second, in some cases, we were able to measure only one CT slice to estimate the L3MA from CT or PET-CT scans before and after chemotherapy. However, we believe that the aforementioned differences had relatively little impact on our results. Third, we were unable to evaluate the physical functions of the patients. Recent studies have defined sarcopenia only as skeletal muscle loss assessed using CT scans, but sarcopenia is based on the function of all muscles rather than muscle mass alone. Therefore, assessing muscle strength and physical performance is vital. Finally, the difference in muscle loss could be a result of differences inherent to the biology of tumors, and not to the difference in treatments. Patients with oncogene-addicted NSCLC (*EGFR* mutation, *ALK* gene rearrangements, *ROS1* mutation, etc.), usually receive molecular targeted therapy as first-line chemotherapy. In this study, there were three patients with *EGFR* mutations or *ALK* gene rearrangements who received cytotoxic chemotherapy as first-line.

Of these, two patients had reduced skeletal muscle while one gained muscle mass. Because of the small number of patients in our sample, we were unable to analyze this discrepancy; however the difference may be associated with differences in treatment. Further studies are needed in order to clarify this point.

In this study, we revealed significant differences in the reduction of skeletal muscle caused by molecular targeted therapy and cytotoxic chemotherapy. In the management of patients with advanced lung cancer, physicians should not only focus on the response rate to chemotherapy but

also consider preserving QOL and physical performance in patients. Further studies are needed to measure the differences in muscular function and physical performance, as well as QOL, between different chemotherapy treatments. Such findings may ultimately yield therapeutic interventions to prevent sarcopenia.

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Disclosure

No authors report any conflict of interest.

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